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 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  SEP 09   CA/CAplus records now contain indexing from 1907 to the
                   present
 NEWS  4  AUG 05   New pricing for EUROPATFULL and PCTFULL effective
                   August 1, 2003
 NEWS  5  AUG 13   Field Availability (/FA) field enhanced in BEILSTEIN
 NEWS  6  AUG 18   Data available for download as a PDF in RDISCLOSURE
 NEWS  7  AUG 18   Simultaneous left and right truncation added to PASCAL
 NEWS  8  AUG 18   FROSTI and KOSMET enhanced with Simultaneous Left and Righ
                   Truncation
 NEWS  9  AUG 18   Simultaneous left and right truncation added to ANABSTR
 NEWS 10  SEP 22   DIPPR file reloaded
 NEWS 11  DEC 08   INPADOC: Legal Status data reloaded
 NEWS 12  SEP 29   DISSABS now available on STN
 NEWS 13  OCT 10   PCTFULL: Two new display fields added
 NEWS 14  OCT 21   BIOSIS file reloaded and enhanced
 NEWS 15  OCT 28   BIOSIS file segment of TOXCENTER reloaded and enhanced
 NEWS 16  NOV 24   MSDS-CCOHS file reloaded
 NEWS 17  DEC 08   CABA reloaded with left truncation
 NEWS 18  DEC 08   IMS file names changed
 NEWS 19  DEC 09   Experimental property data collected by CAS now available
                   in REGISTRY
 NEWS 20  DEC 09   STN Entry Date available for display in REGISTRY and CA/CAplus

 NEWS EXPRESS  NOVEMBER 14 CURRENT WINDOWS VERSION IS V6.01c, CURRENT
               MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
               AND CURRENT DISCOVER FILE IS DATED 23 SEPTEMBER 2003
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
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 NEWS WWW      CAS World Wide Web Site (general information)

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FILE 'HOME' ENTERED AT 14:13:10 ON 10 DEC 2003

=> file caplus medline biosis embase
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6 ANSWER 14 OF 189 CAPLUS COPYRIGHT 2003 ACS on STN

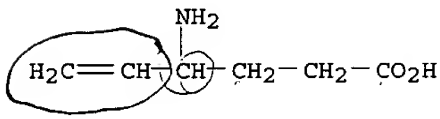
ACCESSION NUMBER: 1999:258894 CAPLUS
DOCUMENT NUMBER: 131:53533
TITLE: Transport of **pregabalin** in rat intestine and Caco-2 monolayers
AUTHOR(S): Jezyk, Nancy; Li, Cheng; Stewart, Barbra H.; Wu, Xiaochun; Bockbrader, Howard N.; Fleisher, David
CORPORATE SOURCE: College of Pharmacy, The University of Michigan, Ann Arbor, MI, 48109-1065, USA
SOURCE: Pharmaceutical Research (1999), 16(4), 519-526
CODEN: PHREEB; ISSN: 0724-8741
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The purpose of this study was to det. if the intestinal transport of **pregabalin** (iso-Bu .gamma.-aminobutyric acid, iso-Bu GABA), a new anticonvulsant drug, was mediated by amino acid carriers with affinity for large neutral amino acids (LNAA). **Pregabalin** transport was studied in rat intestine and Caco-2 monolayers. An in vitro Ussing/diffusion chamber model and an in situ single-pass perfusion model were used to study rat intestinal transport. An in vitro diffusion chamber model was used to evaluate Caco-2 transport. In rat ileum, **pregabalin** transport was saturable and inhibited by substrates of intestinal LNAA carriers including **neurontin** (**gabapentin**), phenylalanine, and proline. Weak substrates of intestinal LNAA carriers (.beta.-**alanine**, .gamma.-aminobutyric acid, and Me aminoisobutyric acid) did not significantly change **pregabalin** transport. In Caco-2 monolayers that showed a high capacity for phenylalanine transport, **pregabalin** transport was concn.- and direction-independent and equiv. in magnitude to the paracellular marker, mannitol. The in vitro and in situ rat ileal permeabilities of the LNAA carrier-mediated compds. **neurontin**, **pregabalin**, and phenylalanine correlated well with the corresponding in vivo human oral absorption. The transport of **pregabalin** was mediated by LNAA carriers in rat ileum but not in Caco-2 monolayers. Caco-2 was not an appropriate model for evaluating the in vivo human oral absorption of **pregabalin** and **neurontin**.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2003 ACS on STN
RN 68506-86-5 REGISTRY
CN 5-Hexenoic acid, 4-amino- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Hexenoic acid, 4-amino-, (.+-.)-
OTHER NAMES:
CN (.+-.)-.gamma.-Vinyl GABA
CN (.+-.)-4-Amino-5-hexenoic acid
CN .gamma.-Vinyl-.gamma.-aminobutyric acid
CN .gamma.-Vinyl-GABA
CN 4-Amino-5-hexenoic acid
CN GVG
CN MDL 71754
CN RMI 71754
CN Sabril
CN **Vigabatrin**
FS 3D CONCORD
DR 60643-86-9
MF C6 H11 N O2
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PHAR, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

4

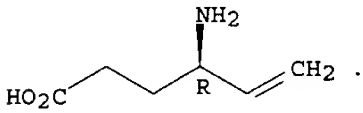


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

619 REFERENCES IN FILE CA (1907 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
620 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L8 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2003 ACS on STN
RN 77162-51-7 REGISTRY
CN 5-Hexenoic acid, 4-amino-, (4R)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Hexenoic acid, 4-amino-, (R)-
OTHER NAMES:
CN (-)-.gamma.-Vinyl GABA
CN **(R)-Vigabatrin**
CN **R-(-)-Vigabatrin**
CN RMI 71894
FS STEREOSEARCH
MF C6 H11 N O2
CI COM
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, CHEMINFORMRX, IMSPATENTS, IMSRESEARCH, IPA, PROMT, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (-).

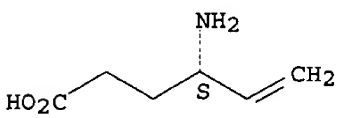


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

26 REFERENCES IN FILE CA (1907 TO DATE)
26 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L8 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2003 ACS on STN
RN 74046-07-4 REGISTRY
CN 5-Hexenoic acid, 4-amino-, (4S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Hexenoic acid, 4-amino-, (S)-
OTHER NAMES:
CN (+)-.gamma.-Vinyl GABA
CN (S)-4-Amino-5-hexenoic acid
CN **(S)-Vigabatrin**
CN 4(S)-Amino-5-hexenoic acid
CN RMI 71890
CN **S-(+)-Vigabatrin**
FS STEREOSEARCH
MF C6 H11 N O2
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CSCHEM, IMSPATENTS, IMSRESEARCH, IPA, PROMT, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

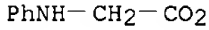
Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

43 REFERENCES IN FILE CA (1907 TO DATE)
44 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 755 OF 756 REGISTRY COPYRIGHT 2003 ACS
RN 103-01-5 REGISTRY
CN Glycine, N-phenyl- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN (Phenylamino)acetic acid
CN Acetic acid, (phenylamino)-
CN Anilinoacetic acid
CN N-(Phenylamino)acetic acid
CN **N-Phenylglycine**
FS 3D CONCORD
MF C8 H9 N O2
CI COM
LC STN Files: BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CSCHEM, DETHERM*, EMBASE, GMELIN*, HODOC*, IFICDB, IFIPAT, IFIUDB, MEDLINE, MRCK*, MSDS-OHS, PIRA, SPECINFO, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



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FILE 'CAPLUS' ENTERED AT 14:13:24 ON 10 DEC 2003
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FILE 'EMBASE' ENTERED AT 14:13:24 ON 10 DEC 2003

=> s lactam
L1 75984 LACTAM

=> s l1 and ((4-amino (s) butanoic) or gabapentin or (aminomethyl (s) cyclohexaneacetic) or pregabalin)
L2 62 L1 AND ((4-AMINO (S) BUTANOIC) OR GABAPENTIN OR (AMINOMETHYL (S) CYCLOHEXANEACETIC) OR PREGABALIN)

=> dup rem l2
PROCESSING COMPLETED FOR L2
L3 46 DUP REM L2 (16 DUPLICATES REMOVED)

=> focus
PROCESSING COMPLETED FOR L3
L4 46 FOCUS L3 1-

=> d ibib abs 1-46

L4 ANSWER 1 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:330417 CAPLUS
DOCUMENT NUMBER: 134:361301
TITLE: The effect of **gabapentin** and **gabapentin-lactam** on retinal ganglion cell survival in an animal model in acute retina ischemia
AUTHOR(S): Jehle, T.; Feuerstein, T. J.; Lagreze, W. A.
CORPORATE SOURCE: Klin, Neuropharmakol., Neurologische Universitatsklinik Freiburg, Germany
SOURCE: Ophthalmologe (2001), 98(3), 237-241
CODEN: OHTHEJ; ISSN: 0941-293X
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: German
AB Redn. in the excitatory and potentially toxic neurotransmitter glutamate can protect retinal ganglion cells. What are the effects of the antiepileptic drug **gabapentin**, for which antiglutamatergic effects were described, and the new substance **gabapentin-lactam** (GBP-L) on retinal ganglion cell survival after retinal ischemia. In 3 groups of 10 rats each, ischemia was induced by elevating the intraocular pressure of the left eye to 120 mm Hg for 1 h. Saline, **gabapentin** (2 x 50 mg/kg i.p.) and GBP-L (2 x 50 mg/kg i.p.) were injected before and 5 h after ischemia. 2 Wk later ischemic damage was quantified histol. by counting the no. of neurons in the ganglion cell layer. In vitro transmitter release expts. were performed to obtain information on the effect of **gabapentin** and GBP-L on ischemia-induced Glu release and the mechanism of action of GBP-L. In the control group 17% of the retinal ganglion cells survived ischemia. GBP-L

doubled the no. of the surviving cells while **gabapentin** was not effective in these expts. In vitro **gabapentin** and GBP-L reduced ischemia-induced Glu release by 35.7 and 42.5%, resp. The blockade of ATP-sensitive K channels antagonized the effect of GBP-L completely. GBP-L is neuroprotective in retinal ischemia and diminishes the release of the excitatory neurotoxic amino acid Glu. The effect of GBP-L might be mediated by ATP-sensitive K channels. Also **gabapentin** reduced Glu release but was not neuroprotective in vivo.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:80040 CAPLUS
DOCUMENT NUMBER: 132:127733
TITLE: Stabilized solid preparations of **4-amino**-3-substituted-**butanoic** acid derivatives and their manufacture
INVENTOR(S): Aomatsu, Akira
PATENT ASSIGNEE(S): Warner Lambert Co., USA
SOURCE: Jpn. Kokai Tokkyo Koho, 34 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2000034227	A2	20000202	JP 1999-133769	19990514
JP 2003055211	A2	20030226	JP 2002-189768	19990514
ZA 2000006483	A	20020409	ZA 2000-6483	20001109

PRIORITY APPLN. INFO.: JP 1998-133112 A 19980515
JP 1999-133769 A3 19990514
OTHER SOURCE(S): MARPAT 132:127733
AB Solid prepns. of H2NCH2CR1R2CH2CO2H [I; R1 = H, OH, Me, Et; R2 = various (un)substituted hydrocarbyl (definitions are described in detail)], useful as nervous system agents for treatment of epilepsy, syncope, head trauma, cerebral dysfunction, Alzheimer disease, Huntington chorea, parkinsonism, etc., are manufd. by adding water-holding agents such as ethylene glycol, propylene glycol, glycerin, etc., and optionally excipients. The prepns. may addnl. contain neutral amino acids. Water-holding agents prevents deterioration of I due to **lactam** formation. **Gabapentin** was spray-coated with an aq. propylene glycol soln. to give powder contg. 0.003% **lactam**. The powder was stored in a sealed container at 60.degree. for 2 wk to show **lactam** content 0.011%, vs. 0.017% for control powder contg. no propylene glycol.

L4 ANSWER 3 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:552622 CAPLUS
DOCUMENT NUMBER: 133:187866
TITLE: **Gabapentin-lactam** (8-aza-spiro[5,4]decan-9-on; GBP-L) inhibits oxygen glucose deprivation-induced [3H]glutamate release and is a neuroprotective agent in a model of acute retinal ischemia
AUTHOR(S): Jehle, Thomas; Lagreze, Wolf A.; Blauth, Eckard; Knorle, Rainer; Schnierle, Peter; Lucking, Carl Hermann; Feuerstein, Thomas J.
CORPORATE SOURCE: Sektion Klinische Neuropharmakologie der Neurologischen Universitatsklinik, Neurozentrum, Freiburg, D-79106, Germany
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (2000), 362(1), 74-81
CODEN: NSAPCC; ISSN: 0028-1298

PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The modulation of the enhanced release of [3H]glutamate following ischemia-like conditions was studied in rat hippocampal slices using a superfusion system. Ischemia was simulated by a glucose-free medium equilibrated with 95% N2 and 5% CO2. In this model the potential neuroprotective effects of several substances on [3H]glutamate release induced by ischemia-like conditions were investigated. **Gabapentin -lactam** (8-aza-spiro-5,4-decan-9-on; GBP-L) was synthesized and patented in the authors' lab. GBP-L (100 .mu.M) reduced the oxygen glucose deprivation-induced [3H]glutamate release by 42.5%, CI95=[33.4%, 51.5%]. The KATP channel antagonist glibenclamide (1 .mu.M) blocked this effect completely. The high antagonist potency was reflected by an apparent pA2-value of glibenclamide of 8.3, CI95=[6.8, 9.4]. Minoxidil sulfate (10 .mu.M), a KATP channel opener, mimicked the effect of GBP-L (inhibition by 22.8%, CI95=[13.2%, 32.5%]). Similarly to its **lactam**, also **gabapentin** (100 .mu.M) reduced the oxygen glucose deprivation-induced [3H]glutamate release by 30.6%, CI95=[15.5%, 45.7%], whereas the "antiglutamatergic" drug riluzole was ineffective. GBP-L and **gabapentin** were also tested in an in vivo model of acute retinal ischemia in rats. The intraocular pressure was elevated for 1 h above the systolic blood pressure. In the control group, 17.5%, CI95=[13%, 22%], of retinal ganglion cells had survived after 2 wk. GBP-L doubled the no. of surviving ganglion cells up to 35%, CI95=[27%, 43%], while **gabapentin** had no effect. This difference between **gabapentin** and its **lactam** may be due to different pharmacokinetic properties. In contrast to the .gamma.-amino acid **gabapentin**, GBP-L is uncharged and therefore might diffuse more easily through biol. membranes, e.g., the plasma membrane, to get access to an intracellular locus of action. Thus, the neuroprotective properties in vivo and the diminished oxygen glucose deprivation-induced [3H]glutamate efflux in vitro of the presumed KATP channel agonist GBP-L suggest that this substance might be therapeutically applied in pathol. situations induced by a rise in extracellular glutamate and/or neuronal cell death.

REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:192914 CAPLUS
DOCUMENT NUMBER: 132:274252
TITLE: **Gabapentin-lactam**, a close analogue of the anticonvulsant **gabapentin**, exerts convulsant activity in amygdala kindled rats
AUTHOR(S): Potschka, Heidrun; Feuerstein, Thomas J.; Loscher, Wolfgang
CORPORATE SOURCE: Department of Pharmacology, Toxicology and Pharmacy, School of Veterinary Medicine, Hannover, D-30559, Germany
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (2000), 361(2), 200-205
CODEN: NSAPCC; ISSN: 0028-1298
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The cyclic GABA analog **gabapentin** (GBP), which recently has been marketed for treatment of epilepsy, is particularly effective against complex-partial seizures as occurring in temporal lobe epilepsy. In the present study, the authors compared the effects of GBP and its **lactam** analog (GBP-L) in the amygdala kindling model of temporal lobe epilepsy. In fully kindled rats, GBP (50 mg/kg and 100 mg/kg i.p.) dose-dependently increased the threshold for focal seizures and inhibited the progression from focal to generalized seizures. This effect was not

assocd. with any marked adverse effects. In contrast, GBP-L (10-50 mg/kg) induced myoclonic activity and generalized clonic seizures in kindled rats, demonstrating a striking qual. difference between the two compds. By comparison with non-kindled rats it was shown that kindling markedly enhanced the sensitivity of rats to the convulsant activity of GBP-L. The finding that the anticonvulsant efficacy of GBP is lost by **lactam** formation indicates that GBP and GBP-L differ in their mechanism(s) of action.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:116875 CAPLUS
DOCUMENT NUMBER: 132:141993
TITLE: Method for making coated **gabapentin** or **pregabalin** particles
INVENTOR(S): Bruna, Etienne; Gendrot, Edouard; Chauveau, Charles; Demichelis, Alain-gilles
PATENT ASSIGNEE(S): Laboratoires Prographarm, Fr.
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000007568	A1	20000217	WO 1999-FR1811	19990723
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2781793	A1	20000204	FR 1998-10091	19980803
FR 2781793	B1	20010720		
CA 2338173	AA	20000217	CA 1999-2338173	19990723
AU 9949160	A1	20000228	AU 1999-49160	19990723
AU 742701	B2	20020110		
EP 1100467	A1	20010523	EP 1999-932956	19990723
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002522375	T2	20020723	JP 2000-563254	19990723
NZ 509980	A	20030725	NZ 1999-509980	19990723
ZA 2001000943	A	20010905	ZA 2001-943	20010202
US 2002012679	A1	20020131	US 2001-777490	20010205
US 6488964	B2	20021203		

PRIORITY APPLN. INFO.: FR 1998-10091 A 19980803
WO 1999-FR1811 W 19990723

AB The invention concerns a method for making coated particles of .gamma.-aminobutyric acid analog whereof the **lactam** content by wt. relative to the wt. of .gamma.-aminobutyric acid analog is less than 0.5 %. The invention is characterized in that it consists in spraying a coating soln. comprising at least a polymer in an org. solvent on said .gamma.-aminobutyric acid analog particles. Agglomerated **gabapentin** (I) particles were coated by a mixt. comprising I 400, PVP-K30 20, and ethanol q.s. 180 mg. The I particles were coated with a soln. comprising Eudragit E 100 280, ethanol 1027, acetone 1027, and colloidal silica 42 mg. The **lactam**:I ratio was 0.07-0.1%.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:603339 CAPLUS
DOCUMENT NUMBER: 138:180523
TITLE: Preferential action of **gabapentin** and **pregabalin** at P/Q-type voltage-sensitive calcium channels: Inhibition of K+-evoked [3H]-norepinephrine release from rat neocortical slices
AUTHOR(S): Dooley, David J.; Donovan, Cindy M.; Meder, Wolfgang P.; Whetzel, Steven Z.
CORPORATE SOURCE: Department of CNS Pharmacology, Pfizer Global Research and Development, Ann Arbor, MI, 48105, USA
SOURCE: Synapse (New York, NY, United States) (2002), 45(3), 171-190
CODEN: SYNAET; ISSN: 0887-4476
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Gabapentin** (GBP; Neurontin) and **pregabalin** (PGB; CI-1008), efficacious drugs in several neurol. and psychiatric disorders, inhibit neurotransmitter release from mammalian brain slices at therapeutically relevant concns. A detailed investigation, exploring the basis for this in vitro phenomenon, focused on norepinephrine (NE) and rat neocortical tissue in complementary assays of neurotransmitter release and radioligand binding. The results are consistent with the hypothesis that GBP, PGB, and related substances decrease neocortical NE release by acting at the .alpha.2.delta. subunit of presynaptic P/Q-type voltage-sensitive Ca2+ channels (VSCC) subserving Ca2+ influx in noradrenergic terminals. The inhibitory action appears competitive with [Ca2+]o and preferential to those neurons undergoing prolonged depolarization. Other results indicate that the redn. of exocytotic NE release is independent of L- and N-type VSCC, classical drug/peptide binding sites on VSCC, Na+ channels, .alpha.2-adrenoceptors, NE transporter, and system L amino acid transporter. These findings suggest a selective modulation of P/Q-type VSCC that are implicated in neurotransmission and several GBP-responsive pathologies.
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:71400 CAPLUS
DOCUMENT NUMBER: 137:134908
TITLE: The neuroprotective properties of **gabapentin -lactam**
AUTHOR(S): Lagreze, Wolf A.; Muller-Velten, Rike; Feuerstein, Thomas J.
CORPORATE SOURCE: Department of Ophthalmology, Albert-Ludwigs University of Freiburg, Freiburg, 79102, Germany
SOURCE: Graefe's Archive for Clinical and Experimental Ophthalmology (2001), 239(11), 845-849
CODEN: GACODL; ISSN: 0721-832X
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Gabapentin-lactam** (GBP-L) is a deriv. of the anti-convulsant drug **gabapentin**. In vitro, GBP-L diminished the hypoxia-induced release of the neurotransmitter and excitotoxin glutamate. This effect could be reversed with glibenclamide, indicating that GBP-L acts as an opener of ATP-sensitive K channels. In vivo, GBP-L was neuroprotective in a rat model of acute retinal ischemia. In this study the authors investigated the time- and dose-effect relationship of this neuroprotection. In each treatment group (n=9), retinal ischemia was

induced in the left eye by pumping air into the anterior chamber to an intraocular pressure of 120 mm Hg for 1 h. Two weeks later, neuronal damage in the ganglion cell layer was histol. quantified. Group 1 received vehicle only; group 2 received 75 mg/kg GBP-L i.p. at the beginning of ischemia; groups 3, 4, 5, 6, and 7 received the same dose at 1, 2, 3, 4, and 5 h after onset of reperfusion. Subgroups 5b and 5c received 50 and 25 mg/kg, resp., 3 h after reperfusion. Each injection was repeated once after 6 h. The proportions of neurons that survived in groups 1 to 7 were 28, 70, 59, 55, 58, 45, and 37%, resp. The proportions of neurons surviving in groups 5b and 5c were 49 and 39%, resp. The difference in neuronal survival between group 1 and groups 2, 3, 4, 5, 5b, and 6 was statistically significant. GBP-L was neuroprotective in an animal model of acute retinal ischemia, even when given .ltoreq. 4 h after reperfusion. GBP-L may prove useful in optic neuropathies such as glaucoma.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 46 MEDLINE on STN
ACCESSION NUMBER: 89258765 MEDLINE
DOCUMENT NUMBER: 89258765 PubMed ID: 2724304
TITLE: Metabolism of 3-(p-chlorophenyl)pyrrolidine. Structural effects in conversion of a prototype gamma-aminobutyric acid prodrug to **lactam** and gamma-aminobutyric acid type metabolites.
AUTHOR: Wall G M; Baker J K
CORPORATE SOURCE: Department of Medicinal Chemistry, School of Pharmacy, University of Mississippi, University 38677.
SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (1989 Jun) 32 (6) 1340-8. Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198907
ENTRY DATE: Entered STN: 19900306
Last Updated on STN: 19900306
Entered Medline: 19890711

AB By use of rat liver or brain homogenate supernatants containing microsomes and/or mitochondria, it was found that the prototype GABAergic prodrug [3-(p-chlorophenyl)pyrrolidine (1)] underwent a series of alpha-oxidation transformations to a pair of amino acid metabolites and a pair of **lactam** metabolites [**4-amino**-3-(p-chlorophenyl) **butanoic** acid, baclofen (5); **4-amino** -2-(p-chlorophenyl)**butanoic** acid (10); 4-(chlorophenyl)pyrrolidin-2-one and 3-(p-chlorophenyl)pyrrolidine-2-one (11)]. With the liver homogenates, the formation of the **lactam** metabolites was approximately 2 orders of magnitude greater than that of the amino acid metabolites, while with the brain homogenates, the amino acid and **lactam** pathways were of similar magnitude. For either tissue, for both the **lactam** and the amino acid series, attack at the less sterically hindered 5-position of the pyrrolidine ring was greater than the attack at the 2-position (5 greater than 10 and 6 greater than 11) with the exception of the liver homogenate mitochondrial fraction (6 less than 11). The parenteral administration of the prodrug 1 was found to give detectable brain levels of 5 as well as activity in an isoniazid-induced (GABA-inhibited) convulsion model.

L4 ANSWER 9 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:23556 CAPLUS
DOCUMENT NUMBER: 138:73534
TITLE: Process for the preparation of 1-(**aminomethyl**)-1-**cyclohexaneacetic** acid
INVENTOR(S): Velardi, Francesco; Fornaroli, Mirco

PATENT ASSIGNEE(S): Procos S.P.A, Italy
SOURCE: U.S. Pat. Appl. Publ., 5 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003009055	A1	20030109	US 2002-156059	20020529
US 6521788	B2	20030218		

PRIORITY APPLN. INFO.: IT 2001-MI1132 A 20010529

AB A process for the prepn. of **gabapentin** (title compd.) comprises: (a) redn. of [1-(nitromethyl)cyclohexyl]acetonitrile to give 3-imino-2-azaspiro[4.5]decan-2-ol, (b) conversion of imino to oxo group by treatment with alkali, (c) redn. of the hydroxyl group , and (d) hydrolysis of the **lactam**. **Gabapentin** hydrochloride (HPLC 99.6%) was passed through a chromatog. column loaded with AMBERLITE IRA 67 to afford **gabapentin** free base.

L4 ANSWER 10 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1991:429916 CAPLUS
DOCUMENT NUMBER: 115:29916
TITLE: Preparation of **lactam**-free 1-aminomethyl-1-carboxymethylcycloalkanes and drug compositions containing them
INVENTOR(S): Augart, Helmut; Gebhardt, Uwe; Herrmann, Wolfgang
PATENT ASSIGNEE(S): Goedecke A.-G., Germany
SOURCE: Eur. Pat. Appl., 8 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 414263	A2	19910227	EP 1990-116265	19900824
EP 414263	A3	19910605		
EP 414263	B1	19941026		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
DE 3928183	A1	19910228	DE 1989-3928183	19890825
JP 03090053	A2	19910416	JP 1990-221422	19900824
JP 3148223	B2	20010319		
ES 2063219	T3	19950101	ES 1990-116265	19900824
US 6054482	A	20000425	US 1995-377618	19950125
BR 2000002663	A	20020219	BR 2000-2663	20000710
JP 2001058976	A2	20010306	JP 2000-270023	20000824

PRIORITY APPLN. INFO.: DE 1989-3928183 A 19890825
US 1990-570500 B1 19900821
JP 1990-221422 A3 19900824
US 1992-865723 B1 19920408
US 1993-20270 B1 19930218
JP 2000-270023 A 20000824

OTHER SOURCE(S): MARPAT 115:29916
GI For diagram(s), see printed CA Issue.

AB Title compds. [I; n = 4-6] contg. <0.5 wt.% of the corresponding **lactams** (II) are prepd. by hydrolyzing II or crude I (obtained from II and still contg. II as an impurity) with concd. HCl until ring opening is complete, optionally followed by incorporating the **lactam**-free I into pharmaceutical compns. contg. excipients that do not catalyze formation of the **lactam**. **Gabapentin** **lactam** in H2O was refluxed with concd. HCl at 108.degree. for 6 h,

the reaction mixt. cooled to 28.degree., the ppt. collected and dissolved in H2O and extd. with CH2Cl2 to give 60% I (n = 5).HCl.

L4 ANSWER 11 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:216888 CAPLUS
DOCUMENT NUMBER: 130:223583
TITLE: Novel stereoselective processes for the preparation of **gabapentin** analogs
INVENTOR(S): Bryans, Justin Stephen; Morrell, Andrew Ian
PATENT ASSIGNEE(S): Warner-Lambert Company, USA
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9914184	A1	19990325	WO 1998-US16652	19980811
W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9887791	A1	19990405	AU 1998-87791	19980811
AU 752444	B2	20020919		
EP 1015415	A1	20000705	EP 1998-939340	19980811
EP 1015415	B1	20030507		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9812351	A	20000919	BR 1998-12351	19980811
JP 2001516738	T2	20011002	JP 2000-511737	19980811
NZ 502786	A	20020531	NZ 1998-502786	19980811
AT 239695	E	20030515	AT 1998-939340	19980811
ZA 9808508	A	19990330	ZA 1998-8508	19980917
US 6465689	B1	20021015	US 1999-445633	19991208
MX 200000063	A	20000831	MX 2000-63	20000103
NO 2000001404	A	20000317	NO 2000-1404	20000317

PRIORITY APPLN. INFO.: US 1997-59204P P 19970918
WO 1998-US16652 W 19980811
OTHER SOURCE(S): CASREACT 130:223583
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB This invention describes novel processes for the stereoselective prepn. of **gabapentin** (1-**aminomethyl**-1-**cyclohexaneacetic** acid) analogs I-III [ring A = A1-A5; R1, R2 = independently H, Me; R3, R4 = independently H, Me; n = 1-4; m = 0-2; X = O, S, S(O), SO2, NR1; R1 = H, (un)branched C1-6 alkyl, CH2Ph, COR2; R2 = (un)branched C1-6 alkyl, CH2Ph, Ph, CO2R3; R3 = (un)branched C1-6 alkyl, CH2Ph, Ph wherein the Ph groups are substituted by 0-3 halo, CF3, or NO2 groups]. Thus, deprotonation of 6.35 mL (31.89 mmol) tri-Et phosphonoacetate with 1.16 g (28.99 mmol) sodium hydride in 40 mL THF, followed by addn. of 3 mL (28.99 mmol) cyclohexanone gave 78% Et cyclohexylideneacetate, which was used without further purifn. The .alpha.,.beta.-unsatd. ester (1.605 g, 9.55 mmol) was dissolved in 30 mL THF and 1.03 mL (19.1 mmol) MeNO2 and 15 mL of 1M Bu4NF in THF (14.0 mmol) added and the mixt. heated to 70.degree. for 18 h to

yield 966 mg (46%) nitro ester IV. The nitro ester (935 mg, 4.08 mmol) was dissolved in 40 mL MeOH and shaken over Raney nickel under a hydrogen atm. at 35.degree. for 18 h to yield 662 mg (100) of **lactam** V. Hydrolysis of the **lactam** (608 mg, 4.0 mmol) with 15 mL 6N HCl and 5 mL dioxane for 4 h gave 682 mg (71%) of desired title compd. VI as the hydrochloride salt. Analogous **gabapentin** analogs were prepd. using 4-methylcyclohexanone, cis-3,5-dimethylcyclohexanone, and (R)-3-methylcyclohexanone.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:736216 CAPLUS
DOCUMENT NUMBER: 137:247921
TITLE: A process for the preparation of cyclic amino acids
INVENTOR(S): Rossi, Paolo; Vecchio, Emilio
PATENT ASSIGNEE(S): C.D. Farmasint S.r.l., Italy
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002074727	A1	20020926	WO 2002-EP2765	20020313
WO 2002074727	B1	20030116		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: IT 2001-MI556 A 20010316
IT 2002-MI103 A 20020122
OTHER SOURCE(S): CASREACT 137:247921; MARPAT 137:247921
AB Cyclic amino acids (CR1R2)nC(CH2NH2)CH2COR3 (R1, R2 = H, alkyl; R3 = OH, NH2, alkoxy; n = 3-11) having high purity, free from the corresponding **lactams** and chloride anions, were obtained by redn. of oxyimino acids (CR1R2)nC(CH:NOH)CH2CO2H. Thus, 10 g 1-(hydroxyiminomethyl) **cyclohexaneacetic** acid (prepd. from cyclohexanecarboxaldehyde and Et bromoacetate) in isopropanol/water was hydrogenated over 5% Rh/Al2O3 at 20.degree. and 9 atm H2 to afford 8.2 g 1-(**aminomethyl**) **cyclohexaneacetic** acid (**gabapentin**) of HPLC purity > 98%.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:935331 CAPLUS
DOCUMENT NUMBER: 136:58826
TITLE: Stable **gabapentin** containing more than 20 ppm of chloride
INVENTOR(S): Singer, Claude; Pilarski, Gideon; Pesachovich, Michael
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

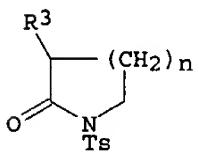
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001097612	A1	20011227	WO 2001-US19100	20010615
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002061931	A1	20020523	US 2001-880854	20010615
US 6531509	B2	20030311		
EP 1289364	A1	20030312	EP 2001-946364	20010615
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2000-211967P P 20000616
WO 2001-US19100 W 20010615

AB Pharmaceutical compns. contg. substantially pure and stable **gabapentin** are disclosed wherein **gabapentin** contains an anion of a mineral acid, such as chloride, in amts. >20 ppm. Thus, a tablet formulation contained **gabapentin** 124 (contg. chloride 5-40 ppm), corn starch 200, microcryst. starch 46, and Sterotex powder 4 g, and water 300 mL. The formulation contained <0.5% **lactam** and after 1 yr of storage at 25.degree. and 60% atm. humidity.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1994:216879 CAPLUS
DOCUMENT NUMBER: 120:216879
TITLE: Aluminum Chloride-Promoted Aminolysis of N-Tosyl **Lactams**
AUTHOR(S): Bon, Eric; Biggs, Dennis C. H.; Bertrand, Guy; Bigg, Dennis C. H.
CORPORATE SOURCE: Laboratoire de Chimie de Coordination, CNRS, Toulouse, F-31077, Fr.
SOURCE: Journal of Organic Chemistry (1994), 59(7), 1904-6
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 120:216879
GI



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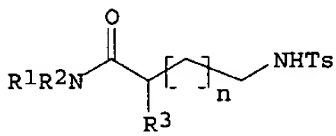


II

AB Aluminum chloride effectively promotes the ring-opening reactions of N-tosyl **lactams** I (R3 = H, Me; n = 1,2,3,9) with amines to give .omega.-aminocarboxamides II (R1, R2 = alkyl, Ph, etc.; same R3).

Hydrolysis of II gave .omega.-amino acids. Redn. of II gave .alpha.,.omega.-diamines. The influence of the size of the **lactam** ring, the environment of the carbonyl group and the nature of the amine were studied. The regioselectivity of the reactions and high yields are rationalized in terms of preferential complexation of the **lactam** carbonyl group with the Lewis acid. Subsequent reactions lead to .omega.-diamines and .omega.-amino acids.

L4 ANSWER 15 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:753060 CAPLUS
DOCUMENT NUMBER: 131:356133
TITLE: Solid compositions containing .gamma.-aminobutyric acid derivatives
INVENTOR(S): Aomatsu, Akira
PATENT ASSIGNEE(S): Warner-Lambert Company, USA
SOURCE: PCT Int. Appl., 99 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9959572	A1	19991125	WO 1999-US10186	19990510
W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2325045	AA	19991125	CA 1999-2325045	19990510
AU 9940733	A1	19991206	AU 1999-40733	19990510
BR 9910494	A	20010109	BR 1999-10494	19990510
EP 1077691	A1	20010228	EP 1999-924164	19990510
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EE 200000671	A	20020415	EE 2000-671	19990510
NO 2000005765	A	20001114	NO 2000-5765	20001114

PRIORITY APPLN. INFO.: JP 1998-133122 A 19980515
JP 1998-133112 A 19980515
WO 1999-US10186 W 19990510
OTHER SOURCE(S): MARPAT 131:356133
AB The present invention provides a stabilized solid compn. contg. a **4-amino**-3-substituted-**butanoic** acid deriv. which can be obtained by incorporating a humectant as a stabilizer. Bulk powders of **gabapentin** (250 g) were sprayed with 72 g water by means of a fluidized granulator and then dried to give **gabapentin** granular powders A. A second batch of bulk powders of **gabapentin** (250 g) were sprayed with a soln. of 5 g propylene glycol in 67 g water by means of the fluidized granulator and then dried to give **gabapentin** granular powders B. The **gabapentin** granular powders A and B obtained were stored under conditions and then the **lactam** formed in each of the powders was detd. by HPLC. E.g., **gabapentin** bulk powders stored for 4 wk at 50.degree. and 85% humidity did not show any degrdn.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:889559 CAPLUS
DOCUMENT NUMBER: 137:363097
TITLE: 2-Pyrrolidinone derivatives substituted at position 4

for reducing the extracellular glutamate level and treating polyglutamine disorders

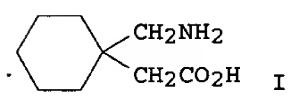
INVENTOR(S): Feurerstein, Thomas J.; Knoerle, Rainer
PATENT ASSIGNEE(S): Germany
SOURCE: U.S. Pat. Appl. Publ., 20 pp., Cont.-in-part of U.S. 6,384,069.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002173537	A1	20021121	US 2002-108879	20020329
US 6384069	B1	20020507	US 2000-554587	20000712

PRIORITY APPLN. INFO.: US 2000-554587 A2 20000712
DE 1997-19751062 A 19971118
WO 1998-EP7383 W 19981117
OTHER SOURCE(S): MARPAT 137:363097

AB 2-Pyrrolidinone derivs. which have in position 4 at least one substituent are described. Methods of treating polyglutamine disorders, e.g. Huntington's disease, dentorubropallidoluysian atrophy, spinal and bulbar muscular atrophy, and spinocerebellar ataxias with 2-pyrrolidinone derivs. are also described. The neuroprotective effect of **gabapentin-lactam** is described.

L4 ANSWER 17 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1992:91232 CAPLUS
DOCUMENT NUMBER: 116:91232
TITLE: The effect of cyclodextrins on the rate of intramolecular lactamization of **gabapentin** in aqueous solution
AUTHOR(S): Kearney, A. S.; Mehta, S. C.; Radebaugh, G. W.
CORPORATE SOURCE: Parke-Davis Pharm. Res. Div., Warner-Lambert Co., Morris Plains, NJ, 07950, USA
SOURCE: International Journal of Pharmaceutics (1992), 78(1), 25-34
CODEN: IJPHDE; ISSN: 0378-5173
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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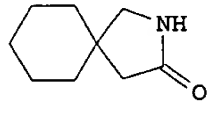


II

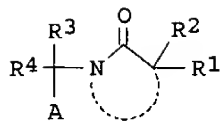
AB The effect of various cyclodextrins on the intramol. lactamization of **gabapentin** (I) in soln. was investigated. Baseline studies in the absence of cyclodextrins were conducted under accelerated conditions to obtain reaction rates that could be followed over a shorter time interval. In aq. buffered solns. at 80.degree. and .mu. = 0.5 M, I undergoes an intramol. aminolysis to yield a stable, cyclized **lactam** product (II) over the pH range of 1.4-11.1. The buffer-independent pH-rate profile was described by two reaction pathways: a specific acid- and specific base-catalyzed lactamization of the uncharged species. Acetate and phosphate buffers were found to catalyze the rate of **lactam** formation, whereas borate had no apparent catalytic effect. Acetate appeared to be acting as a general-acid catalyst, whereas phosphate appeared to be acting as a general-acid and general-base catalyst. Next,

the effect of various cyclodextrins on the lactamization rate was investigated over the pH range of 4.1-7.1. In the pH region defined as specific-acid catalyzed lactamization of the uncharged species, .alpha.- and .gamma.-cyclodextrin had minimal effect on the rate, whereas .beta.- and hydroxypropyl-.beta.-cyclodextrin accelerated the lactamization rate. While in the pH region defined as specific-base catalyzed lactamization of the uncharged species, all four cyclodextrins catalyzed the reaction rate (.beta.- > hydroxypropyl-.beta.- > .alpha.- .apprxeq. .gamma.-cyclodextrin). Interestingly, the catalytic efficiency of acetate buffer varied depending on the cyclodextrin involved. The catalytic efficiency was the greatest in the presence of .beta.-cyclodextrin which was followed by hydroxypropyl-.beta.-cyclodextrin. In 100 mM phosphate buffer of pH 7 and in the presence of varying concns. of the cyclodextrins, the rate of lactamization of I exhibited Michaelis-Menten-type kinetics. The data were consistent with relatively weak drug-cyclodextrin complex formation and with I being more chem. labile as complexed than uncomplexed drug. The enhanced rate obsd. in the presence of cyclodextrins was attributed to complexation-induced, conformational changes in the reactive moieties of I.

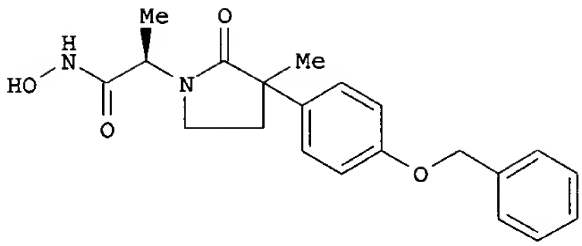
L4 ANSWER 18 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:444499 CAPLUS
DOCUMENT NUMBER: 137:33207
TITLE: Preparation of novel N-substituted-.gamma.,.gamma.-trisubstituted **lactam** derivatives as matrix metalloproteinase inhibitors
INVENTOR(S): Duan, Jingwu; DeCicco, Carl P.; Wasserman, Zelda R.; Maduskuie, Thomas P., Jr.
PATENT ASSIGNEE(S): USA
SOURCE: U.S., 119 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6403632	B1	20020611	US 2000-516709	20000301
US 2003134827	A1	20030717	US 2002-96619	20020312
US 6610731	B2	20030826		

PRIORITY APPLN. INFO.: US 1997-62418P P 19971003
US 1998-165747 A3 19981002
US 2000-516709 A3 20000301
OTHER SOURCE(S): MARPAT 137:33207
GI



I



II

AB Title compds. [I; A is selected from COOH, CH2COOH, CONHOH, SH, CH2SH, PO(OH)2, etc.; ring B is a 4-8 membered cyclic amide contg. 0-3 heteroatoms from O, N, and S, etc.; R1 is phenylmethoxyphenyl, phenoxyphenyl, etc.; R2 is H, CH3, Et, i-Pr, etc.; R1-R2 combine to form heterocyclic; R3 is H, alkylene, heterocyclic, etc.; R4 is H, alkylene, etc.; R3-R4 combine to form heterocyclic], stereoisomer, and pharmaceutically acceptable salt thereof are prepd. as useful metalloprotease inhibitors. For instance, 4-benzyloxyphenyl acetate was sequentially alkylated (THF, NaHMDS) with MeI and allyl bromide to afford the .alpha.,.alpha.-bis(alkylated) deriv. which was converted to the aldehyde (CH2Cl2, O3) and was subsequently reacted with D-alanine Me ester hydrochloride and Zn.degree. in HOAc to yield the **lactam** ester. This intermediate was treated with hydroxylamine to give hydroxamic acid II.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 19 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1995:455254 CAPLUS

DOCUMENT NUMBER: 122:218968

TITLE: Linear and cyclic aliphatic carboxamides of the Murchison meteorite: hydrolyzable derivatives of amino acids and other carboxylic acids

AUTHOR(S): Cooper, G. W.; Cronin, J. R.

CORPORATE SOURCE: Dep. Chemistry Biochemistry, Center Meteorite Studies, Arizona State University, Tempe, AZ, 85287-1604, USA

SOURCE: Geochimica et Cosmochimica Acta (1995), 59(5), 1003-15
CODEN: GCACAK; ISSN: 0016-7037

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Analyses of fractionated aq. exts. of the Murchison meteorite by gas chromatog.-mass spectrometry after silylation with N-methyl-N (tert-butyldimethylsilyl) trifluoroacetamide have revealed an extensive series of linear and cyclic aliph. amides. These include monocarboxylic acid amides, dicarboxylic acid monoamides, hydroxy acid amides, **lactams**, carboxy **lactams**, lactims, N-acetyl amino acids, and substituted hydantoins. Numerous isomers and homologs through at least C8 were obsd. in all cases, except for the N-acetyl amino acids and hydantoins. Carboxy **lactams**, hydantoins, and N-acetyl amino

acids are converted to amino acids by acid hydrolysis, thus, these compds. qual. account for the earlier observation of acid-labile amino acid precursors in meteorite exts. Lab. studies of the spontaneous decompn. of N-carbamyl-.alpha.-amino acids and their dehydration products, the 5-substituted hydantoins, have led to the recognition of a series of aq. phase reactions by which amino acids and cyanic acid/cyanate ion in the primitive parent body might have given rise to several of the obsd. classes of amides, as well as to monocarboxylic acids, dicarboxylic acids, and hydroxy acids. A previously undescribed reaction of 5-substituted hydantoins with cyanic acid/cyanate ion to give carboxamides of the 5-substituent groups was obsd. in the course of these studies. The presence of an extensive suite of amides in a CM chondrite appears to be consistent with the interstellar-parent body formation hypothesis for the org. compds. of these meteorites. The presence of carboxy **lactams** and **lactams** along with free amino acids suggests the possibility of further chem. evolution of meteorite amino acids by thermal polymn. The cyclic amides, given their potential for hydrogen-bonded pair formation, might be considered candidate bases for a primitive sequence coding system.

L4 ANSWER 20 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:253106 CAPLUS
DOCUMENT NUMBER: 125:33249
TITLE: One-step hydroxy substitution of 4,4'-dimethoxybenzhydrol with amides, **lactams**, carbamates, ureas, and anilines
AUTHOR(S): Henneuse, Catherine; Boxus, Thierry; Tesolin, Lorenzo; Pantano, Guiseppe; Marchand-Brynaert, Jacqueline
CORPORATE SOURCE: Laboratoire Chimie Organique Synthese, Universite Catholique Louvain, Louvain-la-Neuve, B-1348, Belg.
SOURCE: Synthesis (1996), (4), 495-501
CODEN: SYNTBF; ISSN: 0039-7881
PUBLISHER: Thieme
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 125:33249
AB A series of amides, **lactams**, carbamates, ureas, and anilines contg. various functionalities were readily N-alkylated with the 4,4'-dimethoxybenzhydryl residue by reaction with 4,4'-dimethoxybenzhydrol in AcOH at room temp. under H2SO4 catalysis.

L4 ANSWER 21 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:940118 CAPLUS
TITLE: Stereochemistry of **gabapentin** and several derivatives: solid state conformations and solution equilibria
AUTHOR(S): Ananda, K.; Aravinda, S.; Vasudev, Prema G.; Raja, K. Muruga Poopathi; Sivaramakrishnan, H.; Nagarajan, K.; Shamala, N.; Balaram, P.
CORPORATE SOURCE: Molecular Biophysics Unit, Indian Institute of Science, Bangalore, 560 012, India
SOURCE: Current Science (2003), 85(7), 1002-1011
CODEN: CUSCAM; ISSN: 0011-3891
PUBLISHER: Current Science Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Gabapentin** (1-(aminomethyl)cycloheaxaneacetic acid; Gpn) is a widely used anti-epileptic drug. The target site of action of Gpn remains controversial. Gpn can exist in two isomeric chair forms. The crystal structures of Gpn 1 and eight derivs., Gpn hydrochloride 2, Gpn **lactam** 3, Boc-Gpn-OH 4, Ac-Gpn-OH 5, Piv-Gpn-OH 6, Tosyl-Gpn-OH 7, Boc-Gpn-OSu 8 and Boc-Gpn-NHMe 9, are described. The aminomethyl group occupies an axial position in 1, 3, 6 and 7, while it lies in an equatorial orientation in 2, 4, 5 and 8. The structure of Boc-Gpn-NHMe 9

reveals that the crystals contain both chair forms of the deriv. in the ratio 0.7:0.3, favoring the aminomethyl group in an axial position. In all cases, the torsional angles about the C.alpha.-C.beta. (.vtheta.1) and C.beta.-C.gamma. (.vtheta.2) bonds of the .gamma.-amino acid residue are characteristic of a gauche, gauche (g, g) conformation. In soln., NMR studies establish rapid conformational exchange, as anticipated, at room temp. Low temp. NMR studies permit conformational freezing and detn. of the free-energy difference between the two 1,1-disubstituted cyclohexane conformers. The largest free-energy difference is obsd. in the free amino acid (0.38 kcal mol-1), with the most stable conformer having the aminomethyl group in the equatorial position. The free-energy difference between the two forms is significantly reduced in the protected derivs., with almost equal populations obsd. in soln. for the fully protected neutral derivs., Boc-Gpn-NHMe and Gpn **lactam**.

L4 ANSWER 22 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1959:11764 CAPLUS
DOCUMENT NUMBER: 53:11764
ORIGINAL REFERENCE NO.: 53:2193h-i,2194a-i,2195a-g
TITLE: Synthesis of 2-azetidinones (.beta.-**lactams**)
AUTHOR(S): Blicke, F. F.; Gould, W. A.
CORPORATE SOURCE: Univ. of Michigan, Ann Arbor
SOURCE: Journal of Organic Chemistry (1958), 23, 1102-7
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
GI For diagram(s), see printed CA Issue.
AB Eight N-substituted .alpha.-phenyl-.beta.-amino acids, obtained by the addn. of an amine to atropic acid (I), as well as a no. of substituted .beta.-amino acids prepd. by other procedures, were converted into 2-azetidinones (II). In some cases esters of the acids were used. A useful method for the synthesis of certain II was found to consist of the interaction of a .beta.-amino acid chloride-HCl with PhNMe2 (III). The general method for the reaction of I to give .beta.-amino acids is as follows. The required amine (0.1 mole) in 50 ml. abs. alc. added to 7.4 g. I in 60 ml. alc., left 4 days, the solvent removed, and the residue recrystd. from a suitable solvent gave the following R1R2C(CO2H)CR3HNHR (IV) (R, R1, R2, R3, % yield, and m.p. given): Me, Ph, H, H, 78, 198-200.degree. (HCl salt, m. 183-4.degree.); CH2:CHCH2, Ph, H, H, 80, 164-5.degree. (HCl salt, m. 168-9.degree.); Me2CH, Ph, H, H, 65, 182-3.degree. (HCl salt, m. 190-1.degree.); C6H11, Ph, H, H, 95, 192-3.degree.; C6H11CH2, Ph, H, H, 95, 200-202.degree. (HCl salt, m. 160-2.degree.); PhCH2, Ph, H, H, 97, 193-5.degree. (HCl salt, m. 174-6.degree.); PhCH2CH2, Ph, H, H, 97, 193-4.degree. (HCl salt, m. 180-1.degree.). .alpha.-Phenyl-.beta.-(dimethylamino)propionic acid was obtained in 80% yield by the above method, m. 143-5.degree. (95% alc.). I (7.4 g.), 9.3 g. PhNH2, and 2 ml. AcOH heated 4 hrs. on the steam bath and purified gave 70% .alpha.-phenyl-.beta.-anilinopropionic acid, m. 128-30.degree. (aq. MeOH). Esters of .alpha.-phenyl-.beta.-(benzylamino)propionic acid (V) and their HCl salts were obtained by a general method previously described (Holley and Holley, C.A. 43, 8357e). The ester-HBr was obtained by addn. of HBr to V in Et2O. The following V were thus obtained (substituent and m.p. or b.p. given): Me, 110.degree./20 mm. (HCl salt, m. 172-3.degree.); Et, 116.degree./20 mm. (HCl salt, m. 169-70.degree.; HBr salt, m. 129-30.degree.); iso-Pr, 46-8.degree. (124.degree./23 mm.) (HCl salt, m. 163-4.degree.); PhCH2, decompd. on attempted distn. (HCl salt, m. 173-4.degree.). H2NCH2CHPhCO2H (VI) (2 g.) gave 2.3 g. H2NCH2CHPhCO2Et.HCl, m. 160-1.degree. (iso-PrOH). N-Methyl-N-nitroso-p-toluenesulfonamide (43 g.) converted to CH2N2 and treated with 16.5 g. VI in 500 ml. Et2O gave 11.5 g. Me ester, b0.5 154-5.degree.. Et .beta.-(benzylamino)propionate (0.2 mole) in 500 ml. H2O refluxed 6 hrs. gave 75% .beta.-(benzylamino)propionic acid, m. 182-4.degree.. Similar hydrolysis of Et .beta.-(benzylamino)butyrate gave 88% .beta.-(benzylamino)butyric acid, m. 179-81.degree.. Me methacrylate

(98.1 g.), 107.0 g. PhCH2NH2, and 500 ml. MeOH left 7 days at room temp., the solvent removed, and the residue distd. gave 123.7 g. Et .alpha.-methyl-.beta.-(benzylamino)propionate (VII), b0.3 97-100.degree.; HCl salt, m. 101-3.degree.. Hydrolysis of VII as above gave 81% free acid, m. 150-2.degree.; HCl salt, m. 131-3.degree.. PhCH(NH2)CH2CO2Et (19.3 g.) in 150 ml. AcOH hydrogenated at 50.degree. in the presence of 0.5 g. PtO2 under an initial pressure of 50 lb./sq. in. until the calcd. amt. of H was absorbed, the filtrate reduced, the residue dissolved in H2O, the soln. made alk., and extd. with Et2O gave after distn. 13.8 g. Et .beta.-cyclohexyl-.beta.-aminopropionate (VIII), b0.4 81-2.degree.; HCl salt, m. 108-10.degree. (iso-PrOH). VIII (39.8 g.) and 12.6 g. PhCH2Cl heated 5 hrs. at 70.degree., refrigerated 12 hrs. with 500 ml. Et2O, and concd. gave 16 g. Et .beta.-cyclohexyl-.beta.-(benzylamino)propionate (IX), b0.1 150-2.degree.. VIII (19.9 g.), 10.6 g. BzH, a catalytic amt. of ZnCl2, and 200 ml. C6H6 refluxed 12 hrs. with azeotropic removal of H2O gave 23 g. Et .beta.-cyclohexyl-.beta.-(benzylideneamino)propionate (X), b1 170.degree.. X (23 g.) in 150 ml. alc. hydrogenated over 0.5 g. PtO2 at 50 lb./sq. in. gave 17.3 g. IX; HCl salt, m. 179-80.degree. (iso-PrOH). IX (16 g.), 4 g. NaOH, and 100 ml. 95% alc. refluxed 12 hrs. gave 74% .beta.-cyclohexyl-.beta.-(benzylamino)propionic acid, m. 165-7.degree.; HCl salt, m. 138-40.degree.. Et cyclohexylcyanoacetate (19.5 g.), 150 ml. AcOH, 5 ml. concd. H2SO4, and 0.2 g. PtO2 hydrogenated under 50 lb./sq. in. pressure gave 17.5 g. Et .alpha.-cyclohexyl-.beta.-aminopropionate (XI), b0.3 76-7.degree.; HCl salt, m. 143-5.degree. (iso-PrOH). XI (19.9 g.) benzylated with 6.3 g. PhCH2Cl gave 10 g. Et .alpha.-cyclohexyl-.beta.-(benzylamino)propionate (XII), b0.2 143-5.degree.; HCl salt, m. 171-3.degree.. XII by similar sapon. gave 78% .alpha.-cyclohexyl-.beta.-(benzylamino)propionic acid, m. 213-14.degree.; HCl salt, m. 230-2.degree.. The HCl salts of IV listed above were obtained by dissolving the amino acid in 10% HCl, evapg. the soln. to dryness, and recrystg. the salts from a suitable solvent. The following IV were also obtained (R, R1, R2, R3, % yield, and m.p. given): PhCH2, H, H, Ph, 78, 185-7.degree.; PhCH2, Me, H, Ph, 67, 170-3.degree.; PhCH2, Me, Me, Ph, 85, 143-5.degree.. II, R1R2C.CHR2.NR.CO, are prepd. by five methods described as follows. Method A. The interaction of Me, Et, iso-Pr, and PhCH2 esters of V with MeMgI and EtMgBr, resp., was studied. In some the molar ratio of the ester and Grignard reagent was 1:1, in others 1:2; the best yield of II (R = PhCH2, R1 = Ph, R2, and R3 = H) was obtained as follows. EtMgBr (from 1.5 g. Mg) added dropwise to 8.9 g. iso-Pr ester of V in 100 ml. Et2O, the mixt. stirred 2 hrs. at room temp., aq. 10% NH4Cl added, the aq. layer sepd., extd. with Et2O, the combined Et2O solns. dried, concd., and the residue placed on a porous plate gave 1.8 g. cryst. material. Et ester of VI (0.05 mole) prepd. from the ester HCl salt allowed to react with 0.15 mole EtMgBr gave II (R = R2 = R3 = H, R1 = Ph). II (1,3-diphenyl) could not be obtained from Me .alpha.-phenyl-.beta.-anilinopropionate and EtMgBr. Method B. The required .beta.-amino acid (0.02 mole) treated with 10 ml. pure SOCl2, the acid chloride HCl suspended in 250 ml. Et2O and added slowly to a soln. of approximately 4 g. CH2N2 in 500 ml. Et2O, the soln. filtered, the ether and excess CH2N2 removed, and the residue either recrystd. or distd. gave II. Method C. The acid chloride-HCl obtained from 0.05 mole of the required acid, IV, and 25 ml. pure SOCl2 suspended in 250 ml. dry C6H6, and added slowly to a refluxing soln. of 18.2 g. dry III in 250 ml. C6H6, the mixt. refluxed 4 hrs., extd. with H2O, the unreacted III removed with 10% HCl, and the C6H6 ext. after drying distd. gave II. Method D. N-Benzyl-.beta.-bromopropionamide (24.2 g.) added to 3 g. NaH and 150 ml. dry PhMe, the mixt. refluxed 12 hrs., cooled, treated with 150 ml. H2O, the aq. layer sepd., extd. with 100 ml. PhMe, the combined PhMe dried, the solvent removed, and the residue distd. gave II. Method E. Products were obtained from the interaction of benzylidenebenzylamine and MeCHBrCO2Et or Me2CBrCO2Et, from benzylidenemethylamine and BrCH2CO2Et or MeCHBrCO2Et, and benzylideneaniline and Et .alpha.-bromophenylacetate. The following II were prepd. by the above methods (R, R1, R2, R3, method, % yield, and m.p. or b.p. given): PhCH2, H, H, H, D, 40, 106-8.degree./1 mm.; PhCH2, H,

H, H, C, O, -; H, Ph, H, H, A, 28, 114-16.degree.; Me, Ph, H, H, C, 25, 86-7.degree./0.1 mm.; CH2:CHCH2, Ph, H, H, C, 48, 103-4.degree./0.1 mm.; Me2CH, Ph, H, H, C, 84, 90-2.degree./0.05 mm.; Me2CH, Ph, H, H, B, 54, -; C6H11, Ph, H, H, C, 44, 59-61.degree.; C6H11CH2, Ph, H, H, C, 80, 50-1.degree.; C6H11CH2, Ph, H, H, B, 31, -; PhCH2, Ph, H, H, C, 72, 70-2.degree.; PhCH2, Ph, H, H, B, 43, -; PhCH2, Ph, H, H, A, 40, -; Ph(CH2)2, Ph, H, H, C, 67, 145-6.degree./0.05 mm.; Ph(CH2)2, Ph, H, H, B, 40, -; PhCH2, Me, H, H, C, 61, 83-4.degree./0.1 mm.; PhCH2, C6H11, H, H, C, 84, 131-2.degree./0.05 mm.; Me, H, H, Ph, .EPSILON., 52, 90-2.degree./0.6 mm.; PhCH2, H, H, Ph, C, 80 138-9.degree./0.1 mm.; PhCH2, H, H, Me, C, 76, 85-6.degree./0.1 mm.; PhCH2, H, H, C6H11, C, 81, 136-7.degree./0.1 mm.; Ph, Ph, H, Ph, C, 7, 132-3.degree.; Me, Me, H, Ph, .EPSILON., 81, 105-6.degree./0.6 mm.; PhCH2, Me, H, Ph, C, 92, 141-2.degree./0.1 mm.; PhCH2, Me, H, Ph, .EPSILON., 76, -; PhCH2, Me, Me, Ph, C, 92, 153-5.degree./0.1 mm., PhCH2, Me, Me, Ph, E, 84, -. II (1-benzyl-3-phenyl) (1.2 g.) in 50 ml. Et2O added dropwise to 0.19 g. LiAlH4 in 30 ml. Et2O, the mixt. refluxed 24 hrs., 0.5 ml. H2O added, the mixt. stirred 4 hrs., filtered, the filtrate dried, and the solvent removed gave 0.9 g. 2-phenyl-3-(benzylamino) propanol (XIII), m. 52-4.degree. (Et2O-ligroine); HCl salt, m. 131-3.degree. (MeCOEt). Et .alpha.-phenyl-.beta.-(benzylamino)propionate (27.4 g.) in 200 ml. Et2O added to 2.3 g. LiAlH4 and 300 ml. Et2O and the mixt. stirred 3 days at room temp. gave 21.8 g. XIII. The CO absorption of each of the II prepd. was found to be within the 1750-1730 cm.-1 range. Since certain N-benzylamides are known to be effective anticonvulsants it was suggested that II may also have anticonvulsant activity.

L4 ANSWER 23 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:865521 CAPLUS
TITLE: A concise synthesis of **gabapentin** via intramolecular C-CH insertion reaction
AUTHOR(S): Chen, Zhenliang; Chen, Zhiyong; Jiang, Yaozhong; Hu, Wenhao
CORPORATE SOURCE: Key Laboratory for Asymmetric Synthesis and Chirotechnology of Sichuan Province, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu, 610041, Peop. Rep. China
SOURCE: Synlett (2003), (13), 1965-1966
CODEN: SYNLES; ISSN: 0936-5214
PUBLISHER: Georg Thieme Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A concise and efficient synthesis of **Gabapentin** was achieved with an overall yield of 56% by 6 N HCl mediated hydrolysis of the corresponding .gamma.-**lactam** (6), obtained from the intramol. C-CH insertion reaction of N-tert-butyl-N-cyclohexylmethyl diazoacetamide (5) with 0.02 mol% Rh2(OAc)4 catalyst.
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 24 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:892740 CAPLUS
TITLE: Process for preparing highly functionalized .gamma.-butyrolactams and .gamma.-amino acids
INVENTOR(S): Blazecka, Peter Garth; Davidson, James Guy, III; Zhang, Ji
PATENT ASSIGNEE(S): Warner-Lambert Company LLC, USA
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003093220	A1	20031113	WO 2003-IB1646	20030417

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003225149	A1	20031204	US 2003-365430	20030213

PRIORITY APPLN. INFO.: US 2002-376991P P 20020430

AB The invention relates to a process for prepg. highly functionalized .gamma.-butyrolactams and .gamma.-amino acids by reductive amination of mucohalic acid or its derivs. and discloses a process for prepg. **pregabalin** or 3-aminomethyl-5-methyloctanoic acid, GABA analogs with desirable medicinal activity. Claimed .gamma.-amino acids have formula R1NHCH2CH(CHR2R3)CH2CO2H [R1 = alkyl, cycloalkyl, (CH2)0-3-aryl, -heterocyclyl, or -heteroaryl; R2, R3 = H, alkyl, alkenyl, cycloalkyl, alkylcycloalkyl, alkoxy, alkylphenyl, alkylphenoxy, or (un)substituted phenyl]. Thus, 1.3 g 5-(benzyloxy)-4-isopropyldihydrofuran-2-one(prepd. from mucochloric or mucobromic acid) was combined with 1.7 g ammonium formate, 0.3 g 20 % Pd/C, and 0.07 g [Ir(COD)Cl]2 in 25 mL MeOH. The mixt. was hydrogenated at 70 .degree.C and 20 psi for approx. 7 h to provide a mixt. of **pregabalin** contaminated with 4-isopropylpyrrolidin-2-one. The mixt. may be submitted to base hydrolysis to provide exclusively **pregabalin**.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 25 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2003:591134 CAPLUS
DOCUMENT NUMBER: 139:149347
TITLE: Methods for producing substituted acrylic acid esters and their use in producing .gamma.-amino acids
INVENTOR(S): Przewosny, Michael Thomas; Puetz, Claudia
PATENT ASSIGNEE(S): Gruenenthal Gmbh, Germany
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003062185	A1	20030731	WO 2003-EP213	20030111

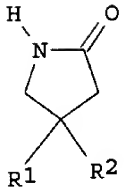
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10203122	A1	20030731	DE 2002-10203122	20020125

PRIORITY APPLN. INFO.: DE 2002-10203122 A 20020125
OTHER SOURCE(S): CASREACT 139:149347; MARPAT 139:149347

GI



I

AB Substituted acrylic acid esters R1(R2)C:CHCO2R [R = (un)branched (un)satd. C1-3 aliph. residue; R1, R2 = H, (un)branched (un)satd. C1-6 aliph. residue; CR1R2 = 5-6-member cycloaliph. ring; e.g., Et cyclohexylidenylactate] are prepd. by the Wadsworth-Emmons-Wittig olefination reaction of aldehydes R1R2CHCHO or ketones R1COR2 (e.g., cyclohexanone) with trialkyl phosphonoacetates (RO)2P(:O)CH2CO2R (e.g., tri-Et phosphonoacetate) in the presence of a base (e.g., aq. potassium carbonate soln.), followed by the addn. reaction of nitromethane to give a satd. nitro ester O2NCH2C(R1)(R2)CH2CO2R [e.g., Et 1-(nitromethyl)cyclohexyl)acetate] which is then subjected to hydrogenation and intramol. cyclocondensation to give a **lactam** [I; e.g., 2-azaspiro[4.5]decan-3-one] which is then subjected to acidic hydrolysis (e.g., aq. HCl) to give the corresponding .gamma.-amino acid H2NCH2C(R1)(R2)CH2CO2H (e.g., **gabapentin** hydrochloride).

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ACCESSION NUMBER: 2000390508 EMBASE

TITLE: [Antidepressants and gabapentinoids - Established and new drugs in the therapy of chronic pain. Preclinical and clinical studies].
ANTIDEPRESSIVA UND GABAPENTINOIDE - ETABLIERTE UND NEUE PHARMAKA IN DER BEHANDLUNG CHRONISCHER SCHMERZEN: PRAKLINISCHE UND KLINISCHE UNTERSUCHUNGEN.

AUTHOR: Eckhardt K.; Feuerstein T.J.

CORPORATE SOURCE: Dr. T.J. Feuerstein, Sekt. Klinische Neuropharmakol., Neurologische Universitatsklinik, Neurozantrum Breisocher Str. 64, D-79106 Freiburg, Germany. feuer@ukl.uni-freiburg.de

SOURCE: Nervenheilkunde, (2000) 19/8 (436-442).
Refs: 30
ISSN: 0722-1541 CODEN: NERVDI

COUNTRY: Germany

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 008 Neurology and Neurosurgery
029 Clinical Biochemistry
037 Drug Literature Index

LANGUAGE: German

SUMMARY LANGUAGE: English; German

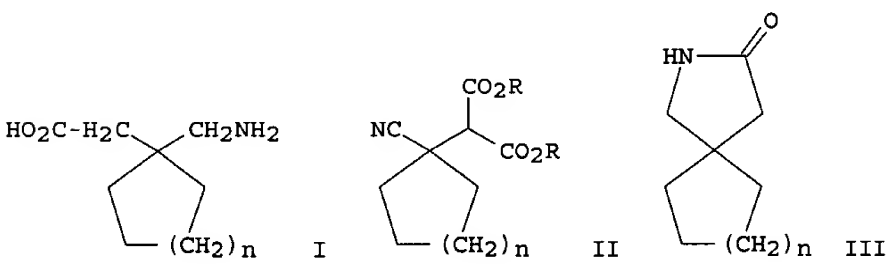
AB Treatment of chronic pain, in contrast to acute pain, remains to be a therapeutic problem. Despite different aetiologic causes sensory neurons develop peripheral and central sensitization in the course of pain chronification resulting in increased sensibility (hyperalgesia and allodynia). Pathophysiological and biochemical changes follow, reflected in an altered expression and function of ion channels and receptors and finally in a changed neuronal phenotype. Tricyclic antidepressants are analgesic in different types of chronic pain (substance of first choice: amitriptyline), in contrast to selective serotonin reuptake inhibitors (SSRIs) with only inconsistent effects in controlled studies. Beside their

known inhibition of monoamine reuptake, tricyclic antidepressants modulate ion channels, among them NMDA receptors, in the dorsal horn of the spinal cord. In controlled clinical studies **gabapentin** reduced pain intensity in patients suffering from chronic pain due to diabetic neuropathy and postherpetic neuralgia. Also **pregabalin** and **gabapentin-lactam** are antinociceptive in animal models of chronic pain. A predominant site of action of these drugs is probably the first nociceptive synapse where they act by diminishing glutamatergic transmission, by enhancing GABAergic transmission and by reducing the activity of nociceptive neurons through K(ATP)channels.

L4 ANSWER 27 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1991:450299 CAPLUS
DOCUMENT NUMBER: 115:50299
TITLE: Preparation of cyclic amino acid derivatives
INVENTOR(S): Steiner, Klaus; Herrmann, Wolfgang; Crone, Guenter; Combs, Charles Shepherd
PATENT ASSIGNEE(S): Goedecke A.-G., Germany
SOURCE: Eur. Pat. Appl., 9 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 414275	A2	19910227	EP 1990-116293	19900824
EP 414275	A3	19910515		
EP 414275	B1	19931208		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
DE 3928184	A1	19910228	DE 1989-3928184	19890825
US 5068413	A	19911126	US 1990-570493	19900821
IL 95480	A1	19950629	IL 1990-95480	19900823
HU 54624	A2	19910328	HU 1990-5333	19900824
HU 208521	B	19931129		
JP 03090054	A2	19910416	JP 1990-221423	19900824
JP 2839344	B2	19981216		
AT 98219	E	19931215	AT 1990-116293	19900824
ES 2059938	T3	19941116	ES 1990-116293	19900824

PRIORITY APPLN. INFO.: DE 1989-3928184 19890825
EP 1990-116293 19900824
OTHER SOURCE(S): CASREACT 115:50299; MARPAT 115:50299
GI



AB The title compds. [I; n = 1-3 integer] are prepd. via alk. hydrolysis of (cyanocycloalkyl)malonates II [R = alkyl], decarboxylating the resulting II [R = H], catalytically hydrogenating the cyano group, and optionally hydrolyzing the byproducts, **lactams** III. II [R = Et, n = 2] was

hydrolyzed with NaOH, the resulting II [R = H, n = 2] in toluene was heated 1 h at 80-85.degree., and the decarboxylated product hydrogenated over 5% Rh/C to give **gabapentin**.

L4 ANSWER 28 OF 46 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:554909 BIOSIS
DOCUMENT NUMBER: PREV200300552167
TITLE: RETINAL GANGLION CELL SURVIVAL IS ENHANCED BY **GABAPENTIN** - **LACTAM** IN VITRO: EVIDENCE FOR INVOLVEMENT OF MITOCHONDRIAL KATP CHANNELS.
AUTHOR(S): Pielen, A. [Reprint Author]; Kirsch, M.; Hofmann, H. D.; Feuerstein, T. J.; Lagreze, W. A. [Reprint Author]
CORPORATE SOURCE: Universitats-Augenklinik, Freiburg, Germany
SOURCE: ARVO Annual Meeting Abstract Search and Program Planner, (2003) Vol. 2003, pp. Abstract No. 5230. cd-rom. Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology. Fort Lauderdale, FL, USA. May 04-08, 2003. Association for Research in Vision and Ophthalmology.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Nov 2003
Last Updated on STN: 26 Nov 2003

AB Purpose: Recently, **Gabapentin**-Laktam (GBP-L) was shown to be neuroprotective in vivo. It has been suggested that it may act by opening ATP-sensitive mitochondrial potassium channels. We tested this hypothesis by quantifying the effect of GBP-L on survival of purified retinal ganglion cells (RGCs) under different conditions. Methods: RGCs were purified from rat retina by immunopanning with antibodies against Thy1.1 and cultured in serumfree N2 medium for 2 days. RGCs were treated with various concentrations (3,2 - 320 muM) of GBP-L with and without glibenclamide (1 muM) or 5-hydroxydecanoate (5-HD, 100 muM). Additional cultures were treated with ciliary neurotrophic factor (CNTF, 50 ng/ml) plus brain derived neurotrophic factor (BDNF, 50 ng/ml) or **gabapentin** (32 muM). Cell survival was quantified by cell counts under phase-contrast microscopy. Results were normalized to controls. Results: GBP-L increased RGC survival to 145%, CI95 (134, 155) in a dose-dependent manner reaching the maximum effect at 32 muM. Preincubation with the KATP channel antagonists glibenclamide (1 muM, blocking both plasmalemmal and mitochondrial KATP channels) or 5-HD (100 muM, blocking selectively mitochondrial KATP channels) blocked this effect: Glibenclamide shifted the dose-response curve of GBP-L to the right, indicating that it acted as a competitive antagonist. The antagonist potency was reflected by a pA2 value of glibenclamide of 6.80, CI95 (5.88, 7.46). 5-HD completely blocked the survival promoting effect of 32 muM GBP-L (98%, CI95 (84, 113)). In comparison, CNTF plus BDNF enhanced survival to 177%, CI95 (158, 196). **Gabapentin**, the parent drug of GBP-L, had no effect on survival (95%, CI95 (82, 108)). Conclusions: GBP-L, but not **gabapentin**, increased survival of RGCs in vitro, possibly by opening mitochondrial KATP channels. These results suggest further testing of GBP-L as a potentially neuroprotective drug.

L4 ANSWER 29 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1976:173604 CAPLUS
DOCUMENT NUMBER: 84:173604
TITLE: Pharmacological properties of .gamma.-aminobutyric acid and its derivatives. IV. Aryl GABA derivatives and their respective **lactams**
AUTHOR(S): Chojnacka-Wojcik, Ewa; Hano, Jozef; Sieroslawska, Janina; Sypniewska, Marta
CORPORATE SOURCE: Dep. Pharmacodyn., Med. Acad., Krakow, Pol.
SOURCE: Archivum Immunologiae et Therapiae Experimentalis

(1975), 23(6), 733-46
CODEN: AITEAT; ISSN: 0004-069X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Pharmacological properties of .alpha.-Phenyl-.gamma.-aminobutyric acid (AFG) [13080-10-9], .beta.-Phenyl-.gamma.-aminobutyric acid (FG) [1078-21-3], and .gamma.-phenyl-.gamma.-aminobutyric acid (GFM) [1011-60-5], phenyl-substituted deriv. of GABA [56-12-2] and their resp. **lactams**, .alpha.-phenyl-.gamma.-aminobutyric acid **lactam** (FP) [6836-97-1], .beta.-phenyl-.gamma.-aminobutyric acid **lactam** (FL) [1198-97-6] and .gamma.-phenyl-.gamma.-aminobutyric acid **lactam** (FM) [22050-10-8] were studied in rats and mice. All compds. diminished spontaneous and pharmacologically potentiated motility, lowered body temp. of mice, and weakened conditioned reflexes in rats. Some of the compds. (AFG, FG, FP) diminished activity of rats in the open-field test and symptoms of amphetamine- (AFG, FG, FP, FL, FM) and apomorphine-induced stereotypy (FL, FG). FG evoked catalepsy and potentiated chloropromazine catalepsy in mice. The compds. potentiated action of narcotic and subthreshold doses of barbituates and ethanol [64-17-5], had analgesic properties, and potentiated analgesic action of morphine [57-27-2]. The most active and least toxic compd. was FG.

L4 ANSWER 30 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:256071 CAPLUS
DOCUMENT NUMBER: 136:284459
TITLE: Stable solid dosage forms of amino acids
INVENTOR(S): Spireas, Spiridon
PATENT ASSIGNEE(S): Sigmapharm, Inc., USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002026263	A2	20020404	WO 2001-US30095	20010926
WO 2002026263	A3	20030103		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002091159	A1	20020711	US 2001-928467	20010813
AU 2001094736	A5	20020408	AU 2001-94736	20010926
EP 1322335	A2	20030702	EP 2001-975405	20010926
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2000-235349P P 20000926
US 2001-928467 A 20010813
WO 2001-US30095 W 20010926
OTHER SOURCE(S): MARPAT 136:284459
AB Pharmaceutical formulations contain an amino acid which is susceptible to the formation of an undesirable **lactam**, and a stabilizer comprising a volatile alc., a nonvolatile alc., a water-immiscible liq. or solid, a liq. with a relatively low dielec. const., liq. and solid surfactants, an antioxidant, a ketone, an aldehyde, a solid polyethylene glycol of high mol. wt., polyvinylpyrrolidone, a derived cellulose, silicon dioxide, or a combination to inhibit the **lactam**

formation. Thus, a formulation contained anhyd. **gabapentin** 400, corn starch 113, and water 100 mg/unit dose.

L4 ANSWER 31 OF 46 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:67173 BIOSIS
DOCUMENT NUMBER: PREV200300067173
TITLE: Process for manufacturing coated **gabapentin** or **pregabalin** particles.
AUTHOR(S): Bruna, Etienne [Inventor, Reprint Author]; Gendrot, Edouard [Inventor]; Chauveau, Charles [Inventor]; Demichelis, Alain-Gilles [Inventor]
CORPORATE SOURCE: Jouy, France
ASSIGNEE: Societe Laboratoires des Products Ethiques - Ethypharm, Houdan, France
PATENT INFORMATION: US 6488964 December 03, 2002
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Dec. 3, 2002) Vol. 1265, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 29 Jan 2003
Last Updated on STN: 29 Jan 2003
AB A process for manufacturing coated particles of gamma-aminobutyric acid analogue, whose **lactam** content by weight relative to the weight of gamma-aminobutyric acid analogue is less than 0.5% is disclosed. The process is characterized in that a coating solution of at least one polymer in an organic solvent is sprayed onto the particles of gamma-aminobutyric acid analogue.

L4 ANSWER 32 OF 46 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2000:248855 BIOSIS
DOCUMENT NUMBER: PREV200000248855
TITLE: **Gabapentin-Lactam**: A novel neuroprotective agent.
AUTHOR(S): Lagreze, W. A. [Reprint author]; Mueller-Velten, R. [Reprint author]; Feuerstein, T. J.
CORPORATE SOURCE: Universitaets-Augenklinik, 79106, Freiburg, Germany
SOURCE: IOVS, (March 15, 2000) Vol. 41, No. 4, pp. S535. print. Meeting Info.: Annual Meeting of the Association in Vision and Opthalmology. Fort Lauderlade, Florida, USA. April 30-May 05, 2000. Association for Research in Vision and Ophthalmology.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Jun 2000
Last Updated on STN: 5 Jan 2002

L4 ANSWER 33 OF 46 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:301172 BIOSIS
DOCUMENT NUMBER: PREV200300301172
TITLE: 13th Meeting of the Network of European CNS Transplantation and Restoration (NECTAR), Amsterdam, Netherlands, December 12-14, 2002.
AUTHOR(S): Anonymous
SOURCE: Cell Transplantation, (2003) Vol. 12, No. 3, pp. 305-327. print.
Meeting Info.: 13th Meeting of the Network of European CNS Transplantation and Restoration (NECTAR). Amsterdam, Netherlands. December 12-14, 2002. European CNS Transplantation and Restoration (NECTAR).
ISSN: 0963-6897.
DOCUMENT TYPE: Conference; (Meeting)

Conference; (Meeting Summary)
LANGUAGE: English
ENTRY DATE: Entered STN: 25 Jun 2003
Last Updated on STN: 25 Jun 2003

AB This meeting on cell transplantation and restoration includes abstracts written in English for 45 presentations. Session themes cover primary fetal dopamine neurons in Parkinson's disease, neuroprotection in Parkinson's disease, transplantation approaches in Huntingdon's disease, neurodegenerative diseases, and stem cell-based neural repair. Selected topics include pawreaching tests in rats, creatine effects, **gabapentin-lactam**, lentiviral vector mediated gene therapy, and activation of endogenous neural precursors.

L4 ANSWER 34 OF 46 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2000:236065 BIOSIS
DOCUMENT NUMBER: PREV200000236065
TITLE: Neuroprotection with **Gabapentin-Lactam** in retinal ischemia: Dose-effect relationship in postischemic treatment.
AUTHOR(S): Mueller-Velten, R. [Reprint author]; Lagreze, W. [Reprint author]; Feuerstein, T.
CORPORATE SOURCE: University Eye Hospital Freiburg, 79106, Freiburg, Germany
SOURCE: IOVS, (March 15, 2000) Vol. 41, No. 4, pp. S14. print.
Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. April 30-May 05, 2000. Association for Research in Vision and Ophthalmology.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Jun 2000
Last Updated on STN: 5 Jan 2002

L4 ANSWER 35 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1964:406367 CAPLUS
DOCUMENT NUMBER: 61:6367
ORIGINAL REFERENCE NO.: 61:1044d-h
TITLE: Correlations between constitution and action of fibrinolysis inhibitors
AUTHOR(S): Lohmann, K.; Markwardt, F.; Landmann, H.
CORPORATE SOURCE: Deut. Akad. Wiss., Berlin-Buch
SOURCE: Thrombosis et Diathesis Haemorrhagica (1964), 10(3/4), 424-30
CODEN: TDHAAT; ISSN: 0340-5338
DOCUMENT TYPE: Journal
LANGUAGE: German

AB cf. CA 59, 10560e. Two tests were used for the evaluation of the antifibrinolytic activity of a no. of .omega.-amino aliphatic and aromatic acids. The 1st was a plasma-lysis test in which the clot-lysis time was measured for the mixt.: 0.2 ml. citrated plasma, 0.1 ml. inhibitor soln., 0.1 ml. streptokinase soln. of 250 units/ml., and 0.1 ml. thrombin soln. of 50 NIH units/ml. The 2nd was the euglobulin lysis test in which human euglobulin was used instead of plasma, and in which the reagents were dissolved in 0.1M tris(hydroxymethyl)aminomethane buffer of pH 7.,5, contg. 0.5% NaCl. The central standard was .epsilon.-aminocaproic acid (I). By substitution at the amino and carboxyl groups the following compds. were synthesized and tested: the N-Ac, N,N-di-Me, N-glycyl, and N-Bz derivs. of I, .epsilon.-guanidinocaproic acid, the Me, Et, Pr, and iso-Pr esters of I, I amide, and I hydrazide. They were all less active than I. The influence of chain length was studied with glycine, .beta.-alanine, .gamma.-aminobutyric acid, .delta.-aminovaleric acid, I, .omega.-aminoenarithic acid, and .omega.-aminoundecanoic acid. I was the most active. Because it seemed to be the distance between the amino and

carboxyl groups that was important, a no. of aromatic .omega.-amino acids with equal distance were studied: p-aminobenzoic acid, 4-amino-1-cyclohexanecarboxylic acid, p-aminomethylbenzoic acid (II), 4-**aminomethyl**-1-cyclohexanecarboxylic acid, p-aminoethylbenzoic acid, 4-aminoethyl-1cyclohexanecarboxylic acid, p-aminophenylacetic acid, 4-amino1-**cyclohexaneacetic** acid, p-aminomethylphenylacetic acid, 4-amino-1-**cyclohexaneacetic** acid, p-aminomethylbenzenesulfonamide, and p-aminobenzenesulfonamide. Most of these compds. were less active than I, except II and its satd. cyclohexane analog, which were more than twice as active as I. To be fully active II had to be added to plasminogen before activation with streptokinase began. Addn. after complete activation did not involve inhibition of plasmin. Hence, II is an inhibitor of plasminogen. It did not inhibit the activation of trypsin, chymotrypsin, papain, bromelin, or the coagulating and esterolytic activities of thrombin.

L4 ANSWER 36 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:678486 CAPLUS
DOCUMENT NUMBER: 139:191463
TITLE: Glucocorticoid blocking agents for increasing blood-brain barrier permeability
INVENTOR(S): Schatzberg, Alan F.; Lindley, Steven; Belanoff, Joseph K.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 15 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003162695	A1	20030828	US 2002-87227	20020227

PRIORITY APPLN. INFO.: US 2002-87227 20020227

AB Glucocorticoid blockers, including glucocorticoid receptor antagonists, are effective to prevent glucocorticoid-induced decrease in permeability of the blood-brain barrier and to increase the permeability of the blood-brain barrier. Administration of glucocorticoid blockers, including glucocorticoid receptor antagonists, concomitant with administration of drugs for treating diseases of the central nervous system increases delivery of such drugs into the central nervous system. Corticosterone decreased blood-brain barrier permeability of haloperidol and clozapine in rats.

L4 ANSWER 37 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:334879 CAPLUS
DOCUMENT NUMBER: 138:343899
TITLE: Gastric-retentive controlled-release oral dosage forms for lower gastrointestinal tract
INVENTOR(S): Berner, Bret; Louie-Helm, Jenny
PATENT ASSIGNEE(S): Depomed, Inc., USA
SOURCE: PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003035041	A1	20030501	WO 2002-US34297	20021025

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG

US 2003104052 A1 20030605 US 2001-24932 20011218
PRIORITY APPLN. INFO.: US 2001-45816 A 20011025
US 2001-24932 A 20011218

AB Controlled release oral dosage forms are provided for the continuous, sustained administration of a pharmacol. active agent to the upper gastrointestinal tract of a patient in whom the fed mode has been induced. The majority of the agent is delivered, on an extended release basis, to the stomach, duodenum and upper regions of the small intestine, with drug delivery in the lower gastrointestinal tract and colon substantially restricted. The dosage form comprises a matrix of a biocompatible, hydrophilic, erodible polymer with an active agent incorporated therein, wherein the polymer is one that both swells in the presence of water and gradually erodes over a time period of hours, with swelling and erosion commencing upon contact with gastric fluid, and drug release rate primarily controlled by erosion rate. Thus, a formulation contained ciprofloxacin-HCl 61.35, Polyox WSR N-60K 14.78, Polyox WSR N-80 21.87, and stearic acid 2%.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 38 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1965:52071 CAPLUS
DOCUMENT NUMBER: 62:52071
ORIGINAL REFERENCE NO.: 62:9244h,9245a-d
TITLE: Synthesis of amino acids of the cyclohexane series and polyamides based on them
AUTHOR(S): Muromova, R. S.; Pletneva, I. D.; Afanas'eva, I. A.; Demidova, T. V.; Pervukhina, I. V.; Shkhiyants, I. V.; Shil'nikova, L. N.
SOURCE: Sintez i Svoistva Monomerov, Akad. Nauk SSSR, Inst. Neftekhim. Sinteza, Sb. Rabot 12-oi [Dvenadtsatoi] Konf. po Vysokomolekul. Soedin. (1964), 1962, 220-5
DOCUMENT TYPE: Journal
LANGUAGE: Russian
GI For diagram(s), see printed CA Issue.
AB The ratio cis-:trans-I (R = Ac, m = 1, n = 0) (II), after the hydrogenation of the corresponding aromatic compd. on a PtO2 catalyst, was 78:22; on Rh-Pt (3:1), almost pure cis-II was obtained. II was hydrolyzed with 20% H2SO4, the mixt. filtered through a column filled with the anion-exchange resin EDE-10P and concd. to give I (R = H, m = 1, n = 0)(III). trans-I(R = Ac, m = 2, n = 0)(IV), m. 197-8.degree., and cis-IV, m. 120-1.degree., were prepd. by the hydrogenation of the corresponding aromatic compd. in the ratio 27.6:65.7 and sepd. by their soly. in cold Me2CO. I(R = H, m = 2, n = 0) (V) was obtained in the same way as III. trans-I(R = Bz, m = n = 1) (VI) (12%), m. 178-8.5.degree., and 30% cis-VI, m. 112.5-13.5.degree., were prepd. by hydrogenation of the corresponding aromatic compd. and sepd. by crystn. from aq. Me2CO. I (R = H, m = n = 1) (VII) was obtained by heating VI in a sealed tube with 10% HCl at 130.degree. 15 hrs. and isolated in the same way as III. The configurations of IV and VI were detd. by the Auwers-Skita rule. The amino acids were heated at 200-320.degree. in a N atm. to give the following polyamides: Polyamides of trans-acids had good thermal stability and were sol. only in concd. H2SO2. , m.p. monomer, m.p. polymer, sp. vilocity; Amino acid, trans-III, -, 516.degree., 0.43; cis-III, -, 385.degree., 0.50; trans-V, 292.degree., 490.degree., 0.67; cis-V, 253.degree., 260.degree., 0.78; trans-VII, 257-9.degree., 423-8.degree.,

0.15; cis-VII, 120.degree., -, -; Polyamides sol. in H2SO4 and cresol were obtained by copolycondensation of trans-III with .epsilon.-capro-**lactam** and trans-V with .vsigma.-enanthic acid (VIII) in cresol or o-hydroxydiphenyl. Thermomech. curves of polyamides of trans-III and trans-V and a copolyamide of trans-V with VIII, were obtained. The polymer of endo-ethylene-.epsilon.-caprolactam melted far lower than the above polyamides.

L4 ANSWER 39 OF 46 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1964:30580 CAPLUS
DOCUMENT NUMBER: 60:30580
ORIGINAL REFERENCE NO.: 60:5353e-h,5354a-d
TITLE: Synthesis and polymerization of 3-azabicyclo[4.3.1]decan-4- one and 7,7-dimethyl-2-azabicyclo[4.1.1]octan-3-one
AUTHOR(S): Hall, H. K. Jr.
CORPORATE SOURCE: E. I. du Pont de Nemours, Wilmington, DE
SOURCE: Journal of Organic Chemistry (1963), 28(11), 3213-14
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
GI For diagram(s), see printed CA Issue.
AB cf. CA 54, 17292e. EtOH (520 ml.) and 2.5 l. C6H6 contg. 315 g. 1: 1 m- and p-HO2CCH2C6H4CH2CO2H (I) refluxed 1 hr. with stirring and the chilled mixt. filtered gave 117 g. almost pure I, m. 255.degree.. The filtered soln. concd., dild. with 1.2 l. EtOH, satd. with dry HCl 20 hrs., and distd. gave 217 g. di-Et phenylenediacetates, b1.1 127-30.degree., hydrogenated in 250 ml. alc. at 135.degree. and 1565 lb./in.2 over 3 g. RuO2 with adsorption of 1.4 moles H, the product (174.5 g., b0.15 115-33.degree.) refluxed (70.0 g.) 5 hrs. with 70 g. NaOH in 500 ml. 2:3 alc.-H2O, the alc. evapd., the residue cooled, acidified with 12N HCl, and kept 3 days, and the ppt. rinsed with H2O gave 51.0 g. air-dried 1,3- and 1,4-cyclohexanediacetic acids, m. 130-2.degree.. The acid mixt. (26.0 g.) and 50 ml. Ac2O distd. 1 hr. with passage of AcOH, the remainder distd. through a Claisen head at 150 mm., the distillate taken up in 100 ml. Et2O and washed with 100 ml. H2O and 150 ml. 15% aq. Na2CO3, the aq. layers extd. with 50 ml. C6H14, the dry org. layers evapd., the residue submitted to short path distn. at 15 mm., the residue crystd. at -80.degree. from C6H14, and the solid (4.6 g.) sublimed at 140.degree./18 mm. yielded 22.6% pure bicyclo[3.3.1]nonan-3-one (II), m. 180-2deg;, .lambda. 1706, 1717 cm.-1; 2,4- dinitrophenylhydrazone m. 208-9.degree. (alc.-EtOAc). Use of BaO in place of Ac2O in the distn. gave a lower yield of II. Esterification of I and hydrogenation of the di-Et ester, m. 59.0-9.5.degree. gave di-Et cyclohexane-1,4-diacetate, hydrolyzed to cyclohexane-1,4-diacetic acid, m. 164-5.degree. and distd. from-BaO without production of ketonic material showed that II was derived from cyclohexane-1,3-diacetic acid. II (12.79 g.) was converted with HONH2 (loc. cit.) to a white solid, m. 108-14.degree., in the receiver to give a crude oxime (12.25 g., b1.0 113-15.degree.), which recrystd. from 30 ml. C6H6 yielded 71.3% oxime (III), m. 108-9.degree.. III (9.92 g.) submitted to Beckmann rearrangement with PhSO2Cl (Gates and Malchick, CA 52, 4507b) gave 6.2 g. **lactam**, subliming at 100-60.degree./0.45 mm., recrystd. from 25 ml. C6H14 at -80.degree. yielded 55.9% 3-azabicyclo[4.3.1]decan-4-one (IV). Similar cyclization of cyclohexane-1,4-diacetic acid gave no bicyclo[3.2.2]nonan-3-one (V). The ketone II can exist in a stable two-chair conformation, whereas V would have a strained boat form of the cyclohexane ring, thus accounting for the difference in ease of formation of the 2 ketones. Com. .beta.-pinene (91% pure "sulfate" pinene, Hercules Powder Co.) ozonized according to Meinwald and Gassman (CA 55, 7314e) gave 99% pure nopinone, b16 92.degree., converted (38.2 g.) to the oxime and distd. to give 40.1 g. material, b1.5 107.degree., recrystd. from 20 ml. C7H16, to yield 33.2 g. nopinone oxime (VI), m. 61.5-5.0.degree.. VI (23.1 g.) submitted to the Beckman rearrangement by using NaOH and PhSO2Cl], the CHCl3 ext. concd. and dild.

with 800 ml. Et2O, the filtered soln. concd. and distd. at 0.3 mm. up to 130.degree., and the solidified distillate sublimed 3 times and crystal. from 15 ml. C7H16 yielded 42.6% 7,7-dimethyl-2-azabicyclo[4.1.1]octan-3-one (VII), m. 111-13.degree., showing an infrared spectrum consistent with that of a **lactam** but no observable 6.50 .mu. band. IV (1.50 g.) heated with a drop of H2O and a drop of 85% H3PO4 8.5 hrs. at 223.degree. in a sealed glass tube under N and the product washed with H2O and Me2CO yielded 88% polyamide of cis-3-aminomethylcyclo-hexylacetic acid, m. 297.degree., inherent viscosity 0.21, in m-cresol. Similar polymerization of VII with 5% 85%. H3PO4 at 200.degree. in 17 hrs. followed by extn. with MeOH yielded 75% polyamide of cis-3-amino-2,2-dimethylcyclobutanepropionic acid, m. 358.degree., inherent viscosity 0.62 in m-cresol. Use of less H3PO4 for longer periods gave lower mol. wt. polymer, and the use of NaH-Ac2O produced only dark oils.

L4 ANSWER 40 OF 46 EMBASE on STN

ACCESSION NUMBER: 1999160109 EMBASE
TITLE: Localized 1H NMR measurements of 2-pyrrolidinone in human brain in vivo.
AUTHOR: Hyder F.; Petroff O.A.C.; Mattson R.H.; Rothman D.L.
CORPORATE SOURCE: F. Hyder, 126 MRC, Yale University, 330 Cedar Street, New Haven, CT 06510, United States. hyder@mrcbs.med.yale.edu
SOURCE: Magnetic Resonance in Medicine, (1999) 41/5 (889-896).
Refs: 30
ISSN: 0740-3194 CODEN: MRMEEN
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
014 Radiology
037 Drug Literature Index
050 Epilepsy
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Localized 1H NMR homonuclear J editing spectroscopy was used to measure the concentration of 2-pyrrolidinone (PRDN) in the human occipital lobe of five normal and six epileptic subjects taking vigabatrin. PRDN is a **lactam** cyclization product of .gamma.-aminobutyric acid (GABA). From a localized volume of 13.5 cm3 in the occipital cortex, the concentration of PRDN ranged from 0.2 to 0.3 .mu.mol/g in normal subjects, whereas in epileptic subjects on vigabatrin PRDN was elevated to 0.6 .+-. 0.1 .mu.mol/g. The elevated PRDN in patients on vigabatrin was in accord with raised GABA levels compared with normals. 1H NMR measurements of PRDN will be important in assessment of the role of this metabolite for improved seizure control.

L4 ANSWER 41 OF 46 EMBASE on STN

ACCESSION NUMBER: 2001341073 EMBASE
TITLE: Pharmacogenomics of drug transporters: The next drug delivery challenge.
AUTHOR: Lee V.H.L.; Sporty J.L.; Fandy T.E.
CORPORATE SOURCE: V.H.L. Lee, Department of Pharmaceutical Sci., University of Southern California, 1985 Zonal Avenue, Los Angeles, CA 90089-9121, United States. vincentl@hsc.usc.edu
SOURCE: Advanced Drug Delivery Reviews, (1 Oct 2001) 50/SUPPL. 1 (S33-S40).
Refs: 39
ISSN: 0169-409X CODEN: ADDREP
PUBLISHER IDENT.: S 0169-409X(01)00186-7
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 022 Human Genetics
030 Pharmacology

037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Scientifically, the third millennium begins with a major triumph - the publishing of the human genomic map, which is destined to have a momentous impact on the quality of life in our time. Disease prevention, individualized medicine, and genotyped-based medicine will soon become a reality. Pharmacogenetics, the forerunner of pharmacogenomics, began in the 1950s with a series of observations relating drug response to various genetic factors. It took almost two more decades for scientists to discover that cytochrome p450 2D6 was responsible for the metabolism of many drugs. This landmark discovery helped focus attention on how gene expression could impact the response to drugs. The stage was set for a revolution in therapeutics some 30 years later as the Human Genome Project crossed the finishing line triumphantly. A parallel development in drug delivery that may also benefit from the fruits of the Human Genome Project is the growing acceptance/awareness of drug transporters as a gateway to epithelial drug transport. This presentation addresses an area in need of attention: the possible impact of genetic polymorphism of drug transporters in pharmacokinetics and the challenge it poses in drug delivery.

L4 ANSWER 42 OF 46 EMBASE
on STN
ACCESSION NUMBER: 2001063213 EMBASE
TITLE: Common infections in older adults.
AUTHOR: Mouton C.P.; Bazaldua O.V.; Pierce B.; Espino D.V.
CORPORATE SOURCE: Dr. C.P. Mouton, Department of Family Practice, Univ. of Texas Hlth. Science Center, 7703 Floyd Curl Dr., San Antonio, TX 78284-7795, United States. mouton@uthscsa.edu
SOURCE: American Family Physician, (15 Jan 2001) 63/2 (257-268). Refs: 40
ISSN: 0002-838X CODEN: AFPYAE
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 017 Public Health, Social Medicine and Epidemiology
020 Gerontology and Geriatrics
027 Biophysics, Bioengineering and Medical Instrumentation
036 Health Policy, Economics and Management
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Infectious diseases account for one third of all deaths in people 65 years and older. Early detection is more difficult in the elderly because the typical signs and symptoms, such as fever and leukocytosis, are frequently absent. A change in mental status or decline in function may be the only presenting problem in an older patient with an infection. An estimated 90 percent of deaths resulting from pneumonia occur in people 65 years and older. Mortality resulting from influenza also occurs primarily in the elderly. Urinary tract infections are the most common cause of bacteremia in older adults. Asymptomatic bacteriuria occurs frequently in the elderly; however, antibiotic treatment does not appear to be efficacious. The recent rise of antibiotic-resistant bacteria (e.g., methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococcus) is a particular problem in the elderly because they are exposed to infections at higher rates in hospital and institutional settings. Treatment of colonization and active infection is problematic; strict adherence to hygiene practices is necessary to prevent the spread of resistant organisms.

L4 ANSWER 43 OF 46 EMBASE
on STN

ACCESSION NUMBER: 1999409703 EMBASE
TITLE: New and future drugs in nerve-gut dysfunction.
AUTHOR: Bueno L.
CORPORATE SOURCE: Prof. L. Bueno, Department of Pharmacology INRA, 180 Chemin de Tournefeuille, 31931 Toulouse Cedex, France. lbueno@toulouse.inra.fr
SOURCE: Italian Journal of Gastroenterology and Hepatology, (1999) 31/8 (794-801).
Refs: 55
ISSN: 1125-8055 CODEN: IJGAFI
COUNTRY: Italy
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB There is increasing evidence that modifications in brain-gut communications are responsible for the occurrence of Functional Bowel Disorders. Based on various experimental models of modified gut sensitivity and the emergence of new pharmacological tools, it is now possible to identify new targets for the corrections of altered brain-gut communications and to improve our understanding of functional gastrointestinal disorders. Both local inflammatory related components and central nervous system acting factors are associated to trigger dysfunctioning and neuropeptides such as tachykinins, bradykinin and calcitonin gene-related peptide are involved in peripheral and spinal sensitization of afferent neurons. Serotonin released from entero chromaffin cells, mast cells, platelets or nerves also play a role, through different receptor subtypes, in initiating gut hypersensitivity. Brain modulation of impaired ascending messages also appears to be an important approach for the correction of symptoms related to gut hyper-responsiveness.

L4 ANSWER 44 OF 46 EMBASE on STN
ACCESSION NUMBER: 2002458611 EMBASE
TITLE: [Gastrointestinal absorption of drugs through the digestive barrier].
SEANCE THEMATIQUE LE FRANCHISSEMENT DES BARRIERES DIGESTIVES.
AUTHOR: Houin G.; Woodley J.
CORPORATE SOURCE: G. Houin, Laboratoire de Pharmacocinetique, CHU Rangueil-Larrey, Avenue Jean Poulhes, F 31403 Toulouse Cedex, France
SOURCE: Annales Pharmaceutiques Francaises, (2002) 60/6 (365-371).
Refs: 21
ISSN: 0003-4509 CODEN: APFRAD
COUNTRY: France
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: French
SUMMARY LANGUAGE: English; French

AB Drug absorption through the digestive membranes occurs essentially by the paracellular route between the cells and through the tight junctions, and by the transcellular route via active or passive transfers across the membrane. Also, active transporters are able to pump substrates from the enterocytes back to the lumen via efflux proteins. These are able to slow and/or to reduce drug absorption, in particular, represent a source of variability by interactions with inducers or inhibitors such as pharmaceutical excipients. Other important factors are solubilization,

drug metabolism, both in the lumen and in the enterocytes, gastric emptying and the interactions with food or between drugs.

L4 ANSWER 45 OF 46 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2002186631 EMBASE
TITLE: A mechanistic approach to understanding the factors affecting drug absorption: A review of fundamentals.
AUTHOR: Martinez M.N.; Amidon G.L.
CORPORATE SOURCE: Dr. M.N. Martinez, Office of New Animal Drug Evaluation, Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, United States
SOURCE: Journal of Clinical Pharmacology, (2002) 42/6 (620-643).
Refs: 151
ISSN: 0091-2700 CODEN: JCPCBR
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB This article provides an overview of the patient-specific and drug-specific variables that can affect drug absorption following oral product administration. The oral absorption of any chemical entity reflects a complex spectrum of events. Factors influencing product bioavailability include drug solubility, permeability, and the rate of in vivo dissolution. In this regard, the Biopharmaceutics Classification System has proven to be an important tool for predicting compounds likely to be associated with bioavailability problems. It also helps in identifying those factors that may alter the rate and extent of drug absorption. Product bioavailability can also be markedly influenced by patient attributes such as the integrity of the gastrointestinal tract, physiological status, site of drug absorption, membrane transporters, presystemic drug metabolism (intrinsic variables), and extrinsic variables such as the effect of food or concomitant medication. Through an awareness of a drug's physicochemical properties and the physiological processes affecting drug absorption, the skilled pharmaceutical scientist can develop formulations that will maximize product availability. By appreciating the potential impact of patient physiological status, phenotype, age, gender, and lifestyle, dosing regimens can be tailored to better meet the needs of the individual patient. .COPYRGT.2002 the American College of Clinical Pharmacology.

L4 ANSWER 46 OF 46 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001268928 EMBASE
TITLE: [Epileptic seizures in the elderly seen from the point of view of neurology and internal medicine].
EPILEPTISCHE ANFALLE IM HOHEREN LEBENSALTER AUS NEUROLOGISCHER UND INTERNISTISCHER SICHT.
AUTHOR: Neundorfer B.; Hahn E.G.
CORPORATE SOURCE: Dr. B. Neundorfer, Neurologische Klinik mit Poliklinik, Universitat Erlangen-Nurnberg, Schwabachanlage 6, 91054 Erlangen, Germany
SOURCE: Internist, (2001) 42/7 (981-990).
Refs: 65
ISSN: 0020-9554 CODEN: INTEAG
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
008 Neurology and Neurosurgery
017 Public Health, Social Medicine and Epidemiology
037 Drug Literature Index

038 Adverse Reactions Titles

LANGUAGE: German